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PATENT
Our Case No.: 10466/127
Genentech, Inc. Case No.: P2548P1C08

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of: Botstein *et al.*

Serial No.: 09/943,664

Filing Date: 8/30/2001

For: SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME

Group Art Unit: 1647

Examiner: Christine J. Saoud

Confirmation No.: 2448

APPEAL BRIEF

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

On July 10, 2008 the Examiner made a final rejection to pending claims 27-34. A Notice of Appeal was filed on November 10, 2008.

Appellant hereby appeals to the Board of Patent Appeals and Interferences from the last decision of the Examiner. A request for a 1 month extension of time is filed concurrently herewith.

The following constitutes Appellant's Brief on Appeal.

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real party in interest is Genentech, Inc.

II. RELATED APPEALS AND INTERFERENCES

The claims pending in the current application are directed to a polypeptide referred to herein as "PRO347." There are no related appeals or interferences. Appellants note however that the related application, U.S. Patent Application Serial No.09/944,896, filed August 31, 2001 (containing claims directed to PRO347 nucleic acids) issued as U.S. Patent No. 7,189,566 on March 13, 2007.

III. STATUS OF CLAIMS

Claims 1-26 and 35-36 have been cancelled. All of the pending claims, claims 27-34, have been finally rejected and are appealed.

Claims 27-34 have been rejected under 35 U.S.C. § 101 as not being supported by a specific, substantial, and credible or by a well-established utility.

Claims 27-34 are rejected under 35 U.S.C. § 112, first paragraph as failing to satisfy the enablement requirement because allegedly one of ordinary skill in the art would not know how to use the claimed polypeptides.

IV. STATUS OF AMENDMENTS

The Response and Request for Reconsideration mailed September 10, 2008 has not been entered, as indicated in the Advisory Action mailed October 8, 2008.

V. SUMMARY OF INVENTION

The present invention is a novel polypeptide identified in the application at issue here, U.S. Patent Application Serial No. 09/943,664, as the "PRO347 polypeptide" (specification pgs. 5, 12-13, 57, 103, 119-137). In particular, the PRO347 polypeptide, encoded by a nucleic acid that is amplified in lung and colon tumors, functions as a therapeutic target and diagnostic marker for lung and colon cancer (specification pgs. 119-137).

More specifically, the invention claimed in the present application is related to a polypeptide isolated from lung or colon tissue comprising the amino acid sequence of the polypeptide of SEQ ID NO:50; the amino acid sequence of the polypeptide of SEQ ID NO:50, lacking its associated signal peptide; the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:50; the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:50, lacking it associated signal peptide; or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209532 (claims 27-32). The invention is further directed to a chimeric polypeptide comprising one of the above polypeptides fused to a heterologous polypeptide (claim 33), and to a chimeric polypeptide wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin (claim 34).

The full-length PRO347 polypeptide having the amino acid sequence of SEQ ID NO:50 is described in the specification at, for example, Example 28, Figure 20 and SEQ ID NO:50. The cDNA nucleic acid encoding PRO347 is described in the specification at, for example, Example 28, Figure 19 and SEQ ID NO:49. Page 21, lines 6-9 of the specification provides the description for Figures 19 and 20. A PRO polypeptide sequence lacking the signal peptide is described in the specification at, for example, pages 22-23. The preparation of chimeric PRO polypeptides, including those wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin, is set forth in the specification at page 53, lines 15-36. Examples 20-23 describe the expression of PRO polypeptides in various host cells, including *E. coli*, mammalian cells, yeast and Baculovirus-infected insect cells. PRO347 is described as a novel polypeptide having a signal peptide sequence and transmembrane domain (see, for example, Example 11 and Figure 20). Finally, Example 28, in the specification at pages 119-137 sets forth a Gene Amplification assay which shows that the PRO347 gene is amplified in the genome of certain human lung and colon cancers (see pages 125-127, Table 10).

VI. ISSUES

The issues to be decided on this appeal are:

1. Whether claims 27-34 are supported by a substantial, specific, and credible utility or a well-established utility, in compliance with 35 U.S.C. § 101?

2. Whether one of ordinary skill in the art would know how to use the polypeptides of claims 27-34 written, in compliance with 35 U.S.C. § 112, ¶ 1?

VII. GROUPING OF CLAIMS

With respect to Issue 1, all claims (claims 27-34) stand and fall together.
With respect to Issue 2, all claims (claims 27-34) stand and fall together.

VIII. SUMMARY OF THE ARGUMENT

Claims 27-34 stand rejected under 35 U.S.C. §101 as allegedly lacking utility. Appellants have previously explained that patentable utility of the PRO347 polypeptides is based upon the gene amplification data for the gene encoding the PRO347 polypeptide. The specification discloses that the gene encoding PRO347 showed significant amplification, ranging from 2 to 8 fold in 22 different lung and colon primary tumors and tumor cell lines, a majority of those tumors and cell lines tested. Indeed, the specification explicitly asserts a diagnostic utility for the PRO347 polypeptides based on the significant gene amplification of PRO347.

To demonstrate the sufficiency of Appellants' asserted utility, Appellants identified U.S. Patent No. 7,208,308, which issued to the assignee of the present application, Genentech, Inc. That patent relies on the same utility asserted by Appellants in the present application and thus provides persuasive evidence of the sufficiency of Appellants' asserted utility. Indeed, at least 16 other patents have issued to Genentech, Inc. with utilities similar to that asserted by Appellants in the present application.

To further support the assertion of utility in the specification, Appellants have submitted numerous declarations. With their Response filed June 26, 2003, Appellants submitted the Declaration of Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample

relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. With their responses submitted 11/25/05 and 6/20/06, Appellants filed the first and second declarations of Paul Polakis, which demonstrate that the gene amplification described in Example 28 more likely than not correlates with protein overexpression. Appellants also filed the Declaration of Randy Scott with their Amendment and Request for Reconsideration filed 12/11/06. The Scott Declaration demonstrates that correlation between mRNA and protein levels is art accepted. The Goddard, Polakis, and Scott declarations demonstrate that one of ordinary skill in the art would find the assertions of utility in the specification specific, substantial, and credible, *i.e.* would find that the claimed PRO347 polypeptides more likely than not have utility as markers for the diagnosis of lung and colon tumors.

The Declaration of Avi Ashkenazi, submitted 12/24/03, makes clear that even if one of ordinary skill in the art doubted the assertion of utility based on gene amplification (which Appellants do not concede), the PRO347 polypeptides still have utility because simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by the real-world example of the breast cancer marker HER-2/neu.

In response to this evidence, the Examiner has argued that the basis of the maintained rejection for alleged lack of utility is "solely that gene amplification levels (genomic DNA levels) are not predictive of mRNA or polypeptide levels." Advisory Action mailed 6/20/07, at page 2. In support of this assertion, the Examiner has cited references by Li, Godbout, Pennica and Konopka as evidence that DNA amplification is not *always* associated with overexpression of the gene product. Final Office Action mailed 7/10/08, at pages 11-14.

Appellants submit that the Examiner applies an improper legal standard in requiring that DNA amplification *always* be associated with overexpression of the gene product.

Appellants respectfully note that statistical certainty is not required. Rather, the evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. The four references cited by the Examiner neither suffice to make a *prima facie* case that more likely than not no generalized correlation exists between gene (DNA) amplification and increased polypeptide levels, nor do they outweigh the evidence demonstrating gene amplification more likely than not correlates with polypeptide overexpression. In particular, the combined teachings of Li, Godbout, Pennica and Konopka are not directed towards genes in general but to a single gene or genes within a single family and thus, their teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA or protein levels.

In contrast, Appellants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. For example, the articles by Pollack *et al.,* Orntoft *et al.*, and Hyman *et al.* (made of record in Appellants' Response filed December 24, 2004) collectively teach that in general, gene amplification increases mRNA expression. Additionally, the Declaration of Dr. Paul Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, shows that, in general, there is a correlation between mRNA levels and polypeptide levels. Taken together, this evidence demonstrates that one of ordinary skill in the art would more likely than not accept Appellants' assertion of utility based on the principle that gene amplification correlates with protein overexpression. Although there are some examples that do not fit within the central dogma of molecular biology that there is a correlation between DNA, mRNA, and polypeptide levels, these instances are exceptions rather than the rule. In the majority of amplified genes, as exemplified by Orntoft *et al.,* Hyman *et al.,* Pollack *et al.,* and the Polakis Declarations, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels.

Therefore, one of skill in the art would reasonably expect in this instance, based on the significant amplification data for the PRO347 gene, that the PRO347 polypeptide is concomitantly overexpressed. Thus, the claimed PRO347 polypeptides have utility in the diagnosis of cancer. Accordingly, Appellants submit that when the proper legal standard is applied, one of ordinary skill in the art would conclude that the present application discloses at least one patentable utility for the claimed PRO347 polypeptides. Appellants respectfully request the rejection of the claims for alleged lack of utility be reversed.

IX. ARGUMENT

Although cancer remains one of the most devastating diseases affecting the world today, many battles in the fight against cancer have been won over the years through development of new techniques for diagnosing and treating cancer. One such development is the present invention, a polypeptide identified in the present application as the "PRO347 polypeptide." In particular, the PRO347 polypeptide, encoded by a nucleic acid that is amplified in lung and colon tumors, functions as a therapeutic target and diagnostic marker for lung and colon cancer.

While recognizing that the nucleic acid encoding PRO347 is supported by a diagnostic utility for lung and colon cancers (*e.g.,* Office Action mailed 9/24/03, p.5; *see also* U.S. Patent No.7,189,566), the Examiner rejects the present invention, the PRO347 polypeptide, for alleged lack of utility. The central dispute in this appeal is the utility of the PRO347 polypeptide.

A. The Utility Rejection Under 35 U.S.C. § 101 Should Be Withdrawn

In the July 10, 2008 Final Rejection and the October 8, 2008 Advisory Action, the Examiner reasserted the rejection of claims 27-34 under 35 U.S.C. § 101, which was first raised in the Office Action mailed March 24, 2003, alleging that the claimed invention is not supported by either a substantial asserted utility or a well established utility. This rejection is maintained despite: (1) Applicants' assertion of utility at pages 119 and 137 of the specification; (2) issuance of U.S. Patent No. 7,208,308 (assigned to the Assignee of the present application, Genentech, Inc.), which claims PRO343 polypeptides and asserts the same utility for the PRO343 polypeptides that is asserted for the PRO347

polypeptides claimed in the present application; (3) issuance of 16 other patents (assigned to Genentech, Inc.) that assert a utility similar to that asserted here; (4) declarations from numerous experts, including Audrey Goddard, Ph.D., Paul Polakis, Ph.D., Randy Scott, Ph.D., and Avi Ashkenazi, Ph.D., explaining why the present invention is supported by a specific, substantial, and credible utility; (5) citation to and reliance on numerous articles demonstrating Appellants' asserted utility is more likely than not; and (6) Appellants' arguments explaining why all of the above evidence demonstrates the utility of the present invention.

The final rejection identifies the remaining issue as "whether [data demonstrating PRO347 gene amplification] makes it more likely than not that the protein encoded by the gene is overexpressed." Office Action mailed 7/10/08, at page 3. In support of this rejection, the Examiner relies on references by Godbout, Li, Konopka, and Pennica and argues that one of ordinary skill in the art would know that amplified levels of PRO347 DNA do not necessarily correlate to overexpression of the encoded PRO347 polypeptide.

Appellants respectfully disagree. As a preliminary matter, Appellants respectfully submit that it is not a legal requirement to establish a necessary correlation between an increase in the copy number of the DNA and protein expression levels that would correlate to the disease state, nor is it imperative to find evidence that DNA amplification is "always" associated with overexpression of the gene product. As discussed below, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is not whether a necessary or even strong correlation between an increase in copy number and protein expression levels exists, but whether it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation. Appellants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Indeed, in rejecting Appellants' assertions of utility, Appellants' arguments and evidence demonstrating utility, and the Goddard, Polakis, Scott and Ashkenazi declarations, the Examiner has set the standard for satisfying the utility requirement too high. Under the

proper utility standard, Applicants have demonstrated that the present invention is supported by a specific, substantial, and credible utility. For example, during prosecution Applicants cited numerous patents and art references which indicate that one of ordinary skill in the art would not have reasonably questioned the utility asserted at pages 119 and 137 of the specification. The references relied on by the Examiner, Godbout, Li, Konopka, and Pennica, do not outweigh the evidence relied on by Appellants. Indeed, the evidence relied on by Appellants demonstrates that consistent with the standards set forth in the *Revised Interim Utility Guidelines Training Materials,* http://www.uspto.gov/web/offices/pac/utility/utilityguide.pdf), the present invention is supported by a specific, substantial, credible utility, and well-established utility.

1. The Legal Standard for Utility

According to 35 U.S.C. § 101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson,* 383 U.S. 519 (1966), the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form." *Id.* at 534.

Later, in *Nelson v. Bowler,* 626 F.2d 853 (CCPA 1980), the CCPA acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility." *Id.* at 856.

In *Cross v. Iizuka,* 753 F.2d 1047 (Fed. Cir. 1985), the CAFC reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between." *Id.* at 1050. The court perceived "[n]o insurmountable difficulty" in finding that, under appropriate circumstances, "*in vitro* testing, may establish a practical utility." *Id.*

This well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001), which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." MPEP § 2107.01. Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, MPEP § 2107 II (B)(1), gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

2. The Examiner Sets the Utility Bar Too High

At pages 119 and 137 of the specification, Applicants assert a specific, substantial, and credible utility for the claimed invention:

> Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers. Therapeutic agents may take the form of antagonists of PRO327, PRO344, PRO347, PRO357 aor (sic) PRO715 polypeptide, for example, murine-human chimeric, humanized or human antibodies against a PRO327, PRO344, PRO347, PRO357, or PRO715 polypeptide. These amplifications are useful as diagnostic markers for the presence of a specific type of tumor.

(p.119)

> The polypeptides encoded by the DNAs tested have utility as diagnostic markers for determining the presence of tumor cells in lung and/or colon tissue samples.

(p.137)

An applicant's assertion of utility creates a presumption of utility sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 183 USPQ 288, 297 (CCPA 1974). *See also In re Jolles*, 206 USPQ 885 (CCPA 1980); *In re Irons*, 144 USPQ 351 (9165); *In re Sichert*, 196 USPQ 209, 212-213 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) *cert. denied*, 469 U.S. 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.

Further, statistical certainty regarding Appellants' assertion of utility is not required to satisfy 35 U.S.C. § 101. *Nelson v. Bowler,* 626 F.2d 853, 856-857, 205 USPQ 881, 883-884 (CCPA 1980). Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed as "wrong" even where there may be some reason to question the assertion. MPEP § 2107.02. Significantly, a 35 U.S.C. § 101 rejection should only be sustained where the asserted utility violates a scientific principle or is *wholly* inconsistent with contemporary knowledge in the art. *In re Gazave,* 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (emphasis added). Indeed, the United States Court of Appeals for the Federal Circuit acknowledges that to fail to satisfy the utility requirement, an invention must be "totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.* , 977 F.2d 1555, 1571 (Fed.Cir. 1992) ("To violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *see also Fuller v. Berger,* 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Appellants' asserted utility should be accepted because it is squarely within the teaching of leading textbooks in the field, and is supported by numerous references and the declarations of skilled experts. This evidence is sufficient to demonstrate utility because an applicants' evidence rebutting the Office's rejection for lack of utility does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility. Moreover, this evidence demonstrates that Appellants' asserted utility does not violate any scientific principle, nor is it wholly inconsistent with contemporary knowledge in the art, nor are the claimed PRO347 polypeptides totally incapable of achieving a useful result. Consideration of the totality of the evidence discussed below clearly demonstrates these points. Thus, the maintained rejection of the present claims for alleged lack of utility is improper and should be withdrawn.

3. The Totality of the Evidence Demonstrates One of Ordinary Skill in the Art Would Accept Appellants' Asserted Utility

Appellants respectfully disagree with the Examiner's assertion that a *prima facie* case of lack of utility is established in the present case. *See* Final Office Action mailed 7/10/08, at page 3. However, even if a *prima facie* case of lack of utility were established (which Appellants do not concede), that showing is overcome by the totality of the evidence, which, as shown below, demonstrates that it is more likely than not that PRO347 gene amplification correlates with PRO347 polypeptide overexpression.

a. It is a Well-Accepted, Scientific Principle that DNA is Transcribed into RNA which is Translated into Protein.

According to Genes V, a ***central dogma*** of molecular biology is that genes are perpetuated as nucleic acid sequences, but function by being expressed in the form of proteins. Thus, genetic information is perpetuated by replication where a double-stranded nucleic acid is duplicated to give identical copies. These copies are then expressed by a two-stage process. First, transcription generates a single-stranded RNA identical in sequence with one of the strands of the duplex DNA. This RNA strand is then translated such that the nucleotide sequence of the RNA is converted into the sequence of amino acids comprising a protein. *See* Lewin, Bejamin. *Genes V.* 1994. Oxford University Press, NY, NY. p. 163. *Genes VI,* the next edition of Lewin's text, further explains that "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI.* 1997. Oxford University Press, NY, NY. pp. 847-848 (Emphasis added). *See* Amendment and Request for Reconsideration filed 12/11/06, Exhibit 1.

Thus, those of skill in the art generally accept that gene expression levels correlate to protein expression levels absent specific events such as translation regulation, post-translation processing, protein degradation, protein isolating errors, etc. *See* Ornstoft *et al.,* "Genome-wide study of gene copy numbers, transcripts, and protein levels in pairs of

non-invasive and invasive human transitional cell carcinomas." 2002. *Molecular & Cellular Proteomics 1.1,* 37-45.

Indeed, another leading treatise, Molecular Biology of the Cell (4th ed. 2002) illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression in Figure 6-3 on page 302. *See* Amendment and Request for Reconsideration filed 12/11/06, Exhibit 1. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Cell 4th at 302 (Emphasis added). Similarly, Figure 6-90 on page 364 of Molecular Biology of the Cell (4th ed) illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Cell 4th at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Cell 4th at 379 (Emphasis added).

Further, Meric *et al.*, *Molecular Cancer Therapeutics*, Vol. 1, 971-979 (2002) states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells…[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (Emphasis added).

See Amendment and Request for Reconsideration filed 12/11/06, Exhibit 1. Appellants respectfully submit that, as these leading treatises demonstrate, those of ordinary skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Therefore, Appellants' assertion that the claimed polypeptides are supported by a diagnostic utility because they are encoded by nucleic acids that are amplified in lung and colon tumors does not violate scientific principles.

b. Appellants' Asserted Utility Relies on the Well-Accepted Scientific Principle that Gene Amplification Correlates with Protein Overexpression

It was well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. Indeed, the working hypothesis among those skilled in the art is that if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. Based on that, Appellants' asserted that the PRO347 polypeptides, which are encoded by a gene amplified in lung and colon tumors, would be useful as "targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers and diagnostic determination of the presence of those cancers." Specification at pages 119 and 137.

Appellants' assertion of utility is based on the overwhelming evidence from the gene amplification data disclosed in the specification, which clearly indicates that the PRO347 nucleic acid is significantly amplified in cancerous tissue compared to normal tissue. Specifically, as explained in Example 28, the inventors identified PRO347 by isolating genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 10, including primary lung and colon tumors of the type and stage indicated in Table 9. As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled. Gene amplification was monitored using real-time quantitative TaqMan™ PCR. Table 10 shows the resulting gene amplification data. Further, Example 28 explains that the results of TaqMan™ PCR are reported in ΔCt units, wherein one unit corresponds to one PCR cycle or approximately a 2-fold amplification relative to control, two units correspond to 4-fold amplification, 3 units to 8-fold amplification etc.

Appellants respectfully submit that a ΔCt value of at least 1.0 was observed for PRO347 in at least 22 of the tumors and tumor cell lines listed in Table 10. PRO347 showed ΔCt values of approximately 1.01 -2.73 in thirteen lung tumors and 1.1-2.1 in nine colon tumors. Thus, Example 28 demonstrates at least 2.00-8.00 fold amplification in 22 lung and colon tumor samples. Accordingly, the present specification clearly discloses overwhelming evidence that the gene encoding the PRO347 polypeptide is significantly amplified in a

number of lung and colon tumors. Based on this data, one or ordinary skill in the art would accept that since the PRO347 gene is amplified, the PRO347 polypeptide would be more likely than not overexpressed. Thus, one of ordinary skill in the art would find it credible that the PRO347 polypeptide is a useful target as a cancer marker for diagnostic determination of the presence of lung and colon tumors.

c. Acceptance of the Same Utility as that Asserted by Appellants to Issue the '308 Patent Demonstrates the Sufficiency of Appellants' Asserted Utility

The USPTO has recognized that Appellants' asserted utility is sufficient by issuing U.S. Patent No. 7,208,308 (the "'308 patent") with claims supported by the same utility as the utility asserted herein. *See, e.g.* claim 1 of the '308 patent, which states that the claimed polypeptide is encoded by a nucleic acid that is amplified in lung or colon tumors.

Issuance of the '308 patent is direct and persuasive evidence that Appellants' assertion of utility satisfies the requirements of 35 U.S.C. § 101. In particular, the protocols and procedures of the gene amplification experiment in the '308 patent (Example 92) and the present application (Example 28) are identical. In addition, the ΔCt values resulting from these gene amplification experiments are similar: 1.0 – 3.82 ΔCt in the '308 patent versus 1.0 – 2.73 ΔCt in the present application.

The Examiner however, alleged issuance of the '308 patent does not provide persuasive evidence that the USPTO accepts Appellants' asserted utility because allegedly in allowing the '308 patent "it is not clear that the utility requirement was considered specific and substantial because of amplification of genomic DNA, or because it was determined that the polypeptide was a serine protease, and therefore the protein had a specific and substantial utility." Office action mailed November 16, 2007, at page 3. However, in response to a rejection for alleged lack of utility, the Applicant of the '308 patent asserted the same utility as that asserted by Appellants: "Applicants have asserted utility for the instantly claimed PRO343 polypeptide based on amplification of the PRO343 gene in the 'gene amplification assay' described in the instant specification in Example 92." *See* '308 Patent, Amendment and Response filed 11/9/05, at page 4. Additionally, the Notice of Allowability for the '308

patent indicates it issued in response to the amendment filed August 15, 2006. *See* '308 Patent, Notice of Allowability, mailed 10/19/06. In the August 15, 2006 Amendment, the Applicants of the '308 patent submitted the Declaration of Randy Scott, Ph.D. *See* '308 patent, Amendment and Response, mailed 8/15/06. In his declaration, Dr. Scott testified about the utility of DNA microarrays, such as that used in Example 92 of the '308 patent, to identify amplified genes. Dr. Scott also testified that in his experience, which includes more than 15 years of personal experience with DNA microarray techniques, gene amplification more likely than not correlates with overexpression of mRNA and ultimately with polypeptide overexpression. *See* '308 patent, Amendment and Response, mailed 8/15/06. Thus, Appellants respectfully submit that the '308 patent issued because the USPTO accepted utility of a polypeptide encoded by an amplified gene.

In addition to relying on the same utility as the '308 patent, during prosecution of the present application, Appellants submitted the same declaration of Randy Scott that was submitted during prosecution of the '308 patent. *See* Amendment and Request for Reconsideration filed 12/11/06. The '308 patent issued because the PTO found the Scott Declaration, along with the other evidence presented during prosecution of the '308 patent, demonstrated that gene amplification more likely than not correlated with mRNA and polypeptide overexpression. As the same evidence has been submitted in support of Appellants' asserted utility, Appellants respectfully maintain that issuance of the '308 patent is persuasive evidence that the present claims are supported by a specific, substantial, and adequate utility and thus, satisfy the requirements of 35 U.S.C. § 101.

The Examiner however, further alleged that issuance of the '308 patent cannot support Appellants' asserted utility because "the actions of one examiner are not binding on another." Advisory Action mailed 6/20/07. Appellants respectfully disagree. Specifically, while Appellants acknowledge that the Examiner is not bound by the actions of another examiner, Appellants maintain that allowance of similar claims is persuasive evidence where those claims are allowed based on the same assertions of utility, and where that same assertion relies on similar data and evidence.

d. Issuance of 16 Other Patents Based on a Similar Utility Also Demonstrates the Sufficiency of Appellants' Asserted Utility

Moreover, the USPTO has acknowledged on more than one occasion that a utility similar to Appellants' asserted utility is sufficient to satisfy the utility requirement of 35 U.S.C. § 101. In addition to issuing the '308 patent, the USPTO has issued 16 other patents, all assigned to Genentech, Inc., assignee of the present application, based on similar assertions of utility. *See e.g.,* U.S. Patent Nos. 7,276,577 (Issued 10/2/07); 7,343,721 (Issued 3/18/08); 7,282,566 (Issued 10/16/07); 7,279,551 (Issued 10/9/07); 7,288,626 (Issued 10/30/07); 7,282,559 (Issued 10/16/07); 7,297,764 (Issued 11/20/07); 7,282,560 (Issued 10/16/07); 7,288,627 (Issued 10/30/07); 7,329,730 (Issued 2/12/08); 7,297,768 (Issued 11/20/07); 7,319,137 (Issued 1/15/08); 7,282,569 (Issued 10/16/07); 7,291,708 (Issued 11/6/07); 7,291,706 (Issued 11/6/07); and 7,348,405 (Issued 3/25/08). Issuance of these 16 patents, which were examined by at least 10 different examiners (two of whom have examined the present application), is direct evidence that Appellants' assertion of utility satisfies the requirements of 35 U.S.C. § 101.

The below claim, which is similar to pending claim 27, issued in U.S. Patent No. 7,276,577:

1. An isolated polypeptide comprising:
    a. the amino acid sequence of the polypeptide of SEQ ID NO:14;
    b. the amino acid sequence of the polypeptide of SEQ ID NO: 14, lacking it associated signal peptide; or
    c. the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203577.

Prior to issuance, this claim was finally rejected and the Assignee of U.S. Patent No. 7,276,577, Genentech, Inc. who is also assignee of the present application, appealed that final rejection. On appeal, the Assignee argued that the above claim was supported by a specific and substantial utility based on microarray data demonstrating amplification of SEQ ID NO:14 in colon, lung and prostate tumors compared to normal tissue. In response, the

USPTO Board of Patent Appeals and Interferences (hereinafter, the "Board") reversed the Examiner's rejection for lack of utility and found "[t]he use of PRO1866 polypeptide as a cancer marker is sufficient to demonstrate utility." *See* Decision of the USPTO Board of Patent Appeals and Interferences, Appeal No. 2006-1469 at pages 9-10. Appellants respectfully submit that finding of the Board demonstrates that the claimed polypeptide, PRO347, also has a sufficient utility, particularly as a cancer marker. Indeed, Appellants assert this specific and substantial utility at paragraph 703 of the present application:

> [0703] This example shows that the PRO327-, PRO344-, PRO347- PRO357-, and PRO715-encoding genes are amplified in the genome of certain human lung, colon and/or breast cancers and/or cell lines. Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers. . . . **These amplifications also are useful as diagnostic markers for the presence of a specific type of tumor type.**

Emphasis added.

The Examiner argued this evidence is not persuasive because these 16 issued patents presented microarray data of mRNA whereas the present application provides data of amplified genomic DNA. Office action mailed 11/16/07, at page 4. Although the data may be different, Appellants respectfully maintain that allowance of these 16 patents still is persuasive evidence that the USPTO at least acknowledges it is more likely than not that overexpression of mRNA correlates with overexpression of the polypeptide. Indeed, in reversing the Examiner's rejection of the claims (for alleged lack of utility) ultimately issued in U.S. Patent No. 7,276,577, the Board stated, "[a]s demonstrated by the Polakis and Smith Declarations, however, there is a strong correlation between mRNA levels and protein expression." Decision of the USPTO Board of Patent Appeals and Interferences, Appeal No. 2006-1469 at page 9. As discussed more fully below, Appellants submitted the same Polakis Declarations in this case that were submitted during prosecution of U.S. patent No. 7,276,577. *See* Request for Reconsideration filed 11/25/05.

e. The Numerous Declarations Submitted in Support of Appellants' Asserted Utility Demonstrate One of Ordinary Skill in the Art Would Accept Appellants' Assertion of Utility for PRO347 Polypeptides

Appellants have submitted numerous declarations that demonstrate the claimed polypeptides are supported by an adequate utility.

(1) The Goddard Declaration

In support of Appellants' assertion that the Example 28 demonstrates significant gene amplification of the PRO347 nucleic acid, Appellants submitted with their Response filed June 26, 2003, a Declaration by Dr. Audrey Goddard. Appellants particularly draw the Board's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.,* non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

As indicated above, the gene encoding the PRO347 polypeptide shows significantly higher than a two-fold amplification in a majority of the tumors and tumor cell lines tested. In addition, the Goddard Declaration clearly establishes that the TaqMan real-time PCR method described in Example 28 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Goddard Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO347 is a diagnostic marker of lung and colon cancer.

(2) The Polakis Declarations

Appellants also submitted two declarations by Paul Polakis, Ph.D. in support of the assertion of utility. In his first declaration, Dr. Polakis declared that in general, there is a correlation between mRNA levels and polypeptide levels. *See* Request for Reconsideration filed 11/25/05. More specifically, Dr. Polakis explains:

> 4. In the course of the research conducted by Genentech's Tumor Antigen Project . . . using microarray analysis, we have identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, we have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. We have then compared the levels of mRNA and protein in both the tumor and normal cells analyzed.
>
> 5. From the mRNA and protein expression analyses described in paragraph 4 above, we have observed that there is a strong correlation between changes in the level of mRNA present in any particular cell type and the level of protein expressed from that mRNA in that cell type. In approximately 80% of our observations we have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells.
>
> 6. Based upon my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.

Significantly, Dr. Polakis declared that "in approximately 80%" of the cases observed in connection with the Tumor Antigen Protein, increases in the mRNA levels correlated with changes in the levels of protein expression. Thus, this is direct evidence that gene amplification more likely than not correlates with protein overexpression. Indeed, according to MPEP § 2107, the Examiner "must accept an opinion from a qualified expert that is based on relevant facts whose accuracy is not being questioned; it is

improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." (emphasis added).

With the Amendment and Request for Continued Examination filed June 20, 2006, Appellants submitted a second Declaration of Paul Polakis that included data establishing that more than 90% of the genes identified as being amplified in the Tumor Antigen Project referenced in the Polakis Declarations (Example 28 in the present application is based on the Tumor Antigen Project referenced in the Polakis Declarations) were detectably overexpressed in human tissue compared to normal tissue at both the mRNA and protein levels. More specifically, Appellants direct the Board's attention to paragraph 5 of the Second Declaration of Dr. Polakis, where Dr. Polakis declares that the data provided therein indicates that:

> of the 31 genes identified as being detectably overexpressed in human tumor tissue as compared to normal tissue at the mRNA level, 28 of them (i.e., greater than 90%) are also detectably overexpressed in human tumor tissue as compared to normal human tissue at the protein level. As such, in cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA.

Second Declaration of Paul Polakis submitted June 20, 2006, at Paragraph 5, Exhibit B.

The Polakis Declarations are persuasive evidence of how one of ordinary skill in the art would view Applicant's assertion of utility, which is based on the art accepted correlation between gene amplification and protein overexpression.

(3) The Scott Declaration

Appellants also submitted a declaration by Randy Scott, Ph.D., in support of their assertion of utility for the PRO347 polypeptides. *See* Amendment and Request for Reconsideration filed 12/11/06. Dr. Scott was a co-founder of Incyte Pharmaceuticals, Inc., the world's first genomic information business, and is currently the Chairman and Chief Executive Officer of Genomic Health, Inc., a life science company located in Redwood City, California, which provides individualized information on the likelihood of disease recurrence and response to certain types of therapy using gene expression

profiling. Based on his more than 15 years of personal experience with the DNA microarray technique and its various uses in the diagnostic and therapeutic fields, and his familiarity with the relevant art, ***Dr. Scott unequivocally confirms that, as a general rule, there is a good correlation between mRNA and protein levels in a particular tissue***. Appellants respectfully direct the Board's attention to paragraph 10 of the Scott Declaration:

> One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, **it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue**. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, **without the need to directly measure individual protein expression levels.**

(emphasis added).

In the Office action mailed March 7, 2007, the Examiner rejected the Scott Declaration as unpersuasive because in the Examiner's view the Scott Declaration sets forth conclusions, not facts, and because it is outweighed by the totality of the evidence. Appellants respectfully disagree with those characterizations. In his declaration, Dr. Scott unequivocally confirms that, as a general rule, there is a good correlation between mRNA and protein levels in a particular tissue. This conclusion, which states a general rule observed over time is based on the stated facts that Dr. Scott has more than 15 years experience with microarray technologies, and in his experience, Dr. Scott has noticed a good correlation. Appellants respectfully submit that when the Scott Declaration is considered with the other evidence cited by Appellants supporting the asserted utility, as it must be, it is clear that Appellants have met the burden of establishing a utility for the claimed polypeptide. Indeed, as Appellants noted above, the Scott Declaration was submitted along with the response that led to issuance of the '308 patent.

(4) The Ashkenazi Declaration

Finally, Appellants submitted declaratory evidence demonstrating Appellants' claimed invention is supported by an adequate utility even if the Board finds one of ordinary skill in the art would not find it more likely than not that gene amplification correlates with protein overexpression (a point which Appellants do not concede). Appellants submitted a declaration by Avi Ashkenazi, Ph.D. and an article by Hanna and Mornin (Pathology Associates Medical Laboratories, August 1999) with their Amendment and Response filed 12/24/03, which demonstrates utility of the claimed polypeptides because simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. As Dr. Ashkenzi explains, this leads to better determination of a suitable therapy for the tumor as demonstrated by the real-world example of the breast cancer marker HER-2/neu. Appellants respectfully submit that this is a substantial utility (separate from the substantial utility based on correlation between gene amplification and protein overexpression) adequate to satisfy the utility requirement of 35 U.S.C. § 101. Indeed, according to § 2107 of the MPEP, "any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility.

f. Utility of the Claimed Polypeptides is Not Inconsistent with Knowledge in the Art

In addition to providing evidence of issued patents relying on the same or similar assertions of utility, numerous declarations establishing the significance of the PRO347 gene amplification and correlation of mRNA and polypeptide expression levels, throughout prosecution Appellants have cited more than 140 references demonstrating that gene amplification more likely than not correlates with protein overexpression. *See, e.g.,* Response and request for Continued Examination mailed 12/11/06. These references cited by Appellants demonstrate that one of ordinary skill in the art would reasonably conclude that the present invention is supported by a specific, substantial, and credible utility.

(1) Gene Amplification More Likely Than Not Correlates with mRNA Overexpression

Indeed, references by Pollack *et al.*, Ornoft *et al.*, Hyman *et al.*, Varis and Bermont demonstrate that gene amplification more likely than not correlates with increased mRNA expression. Specifically, Pollack *et al.* profiled DNA copy number alterations across 6,691 mapped human genes in 44 breast tumors and 10 breast cancer cell lines and reported that microarray measurements of mRNA levels revealed remarkable degrees to which variation in gene copy number contributes to variation in gene expression in tumor cells. *See* Pollack *et al.*, "Microarray analysis reveals a major direct role of DNA copy number alteration in the transcriptional program of human breast tumors." 2002. *PNAS,* 99(20):12963-12968. Pollack *et al* further report that their findings that DNA copy number plays a role in gene expression levels are generalizable. Thus significantly, "[t]hese findings provide evidence that widespread DNA copy number alteration can lead directly to global deregulation of gene expression, which may contribute to the development or progression of cancer."

In particular, Pollack *et al.* report a parallel analysis of DNA copy number and mRNA levels. Pollack *et al.* found that "[t]he overall patterns of gene amplification and elevated gene expression are *quite concordant, i.e.*, a significant fraction of highly amplified genes appear to be correspondingly highly expressed." (emphasis added). Specifically, of 117 high-level DNA amplifications 62% were associated with at least moderately elevated mRNA levels and 42% were found associated with comparably highly elevated mRNA levels.

Ornoft *et al.* report similar findings in "Genome-wide study of gene copy numbers, transcripts, and protein levels in pairs of non-invasive and invasive human transitional cell carcinomas." 2002. *Molecular & Cellular Proteomics 1.1,* 37-45. Initially, Ornoft *et al.* note that "[h]igh throughput array studies of the breast cancer cell line BT474 ha(ve) suggested that there is a correlation between DNA copy numbers and gene expression in highly amplified areas ( ), and studies of individual genes in solid tumors have revealed a good correlation between gene dose and mRNA or protein levels in the case of c-erb-B2, *cyclin d1, ems1,* and N-myc." Ornoft *et al.*, at p. 37.

Specifically, Orntoft *et al.* used 2D-PAGE analysis on four breast tumor tissue samples to determine correlation between genomic and protein expression levels of 40 well resolved, known proteins. Orntoft reported that "[i[n general there was a *highly significant correlation* ($p<0.005$) between mRNA and protein alterations ( ). Only one gene showed disagreement between transcript alteration and protein alteration." (emphasis added). Orntoft *et al.,* at p. 42. Additionally, Orntoft *et al.* report that "11 chromosomal regions where CGH showed aberrations that corresponded to the changes in transcript levels also showed corresponding changes in the protein level ( )." Orntoft *et al.,* at p. 43. The regions examined by Orntoft include genes encoding proteins that are often found altered in bladder cancer.

Orntoft *et al.* note that their study reports a *striking correspondence* between DNA copy number, mRNA expression and protein expression. Orntoft *et al.*, further note that any observed discrepancies in correlation may be attributed to translation regulation, post-translation processing, protein degradation or some combination of these.

However, the Examiner rejected Appellants' reliance on Orntoft because allegedly Orntoft looked at "regions of chromosomes with clusters of chromosomal material containing strong gains." Office action mailed 7/10/08 at page 8. Additionally, the Office action asserts that "[i[f PRO347 is not part of a cluster showing strong gains, then the findings of Orntoft are not applicable." *Id.* Appellants respectfully disagree. Appellants rely on Orntoft for the teaching that in general gene amplification correlates with polypeptide overexpression. Orntoft clearly teaches this correlation as discussed above.

Similarly Hyman *et al.,* compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. *See* Hyman *et al.,* "Impact of DNA amplification on gene expression patterns in breast cancer." 2002. *Cancer Research,* 62:62-40-6245.

The Examiner also disagrees with Appellants' reliance on Hyman and argued that "[s]ince Hyman et al found that less than half of the amplified genes were overexpressed

at the mRNA level" Hyman supports the Office's position. Office action mailed 7/10/08, at page 9. Appellants respectfully disagree. Hyman reports that "[t]hroughout the genome, both high- and low-level copy number changes had a substantial impact on gene expression, with 44% of the highly amplified genes showing overexpression." Abstract. Hyman concludes that the disclosed analysis provided: "(a) evidence of a prominent global influence of copy number changes on gene expression levels; (b) a high-resolution map of 24 independent amplicons in breast cancer; and (c) identification of a set of 270 genes, the overexpression of which was statistically attributable to gene amplification." Page 5. Hence, Hyman teaches gene amplification correlates with protein overexpression.

Varis and Bermont are yet further examples that utility of the present invention based on a correlation between gene amplification and protein overexpression is not wholly inconsistent with knowledge in the art. Varis *et al.*, carried out a comprehensive analysis of gene copy number and expression levels of 636 chromosome 17-specific genes in gastric cancer. *See* Varis *et al.*, "Targets of gene amplification and overexpression at 17q in gastric cancer." *Cancer Res.* 2002. 1;62(9):2625-9. Specifically, Varis *et al.* report that analysis of DNA copy number changes by comparative genomic hybridization on a cDNA microarray revealed increased copy numbers of 11 genes, 8 of which were found to be overexpressed in the expression analysis. Thus, Varis *et al.*, teach there is a 72% correlation between increased DNA copy number and gene expression level.

Bermont teaches that overexpression of p185 is usually associated with c-erbB-2 amplification. Specifically, Bermont reports that 100% of the overexpressed p185 protein in 106 breast cancer samples studied also displayed c-erbB-2 amplification. *See* Bermont *et al.*, "Relevance of p185 HER-2/neu oncoprotein quantification in human primary breast carcinoma." *Breast Cancer Res Treat.* 2000 63(2):163-9. *See also* Hu *et al.*, "Profiling of differentially expressed cancer-related genes in esophageal squamous cell carcinoma (ESCC) using human cancer cDNA arrays: overexpression of oncogene MET correlates with tumor differentiation in ESCC." *Clin Cancer Res.* 2001 7(11):3519-25 (the results of cDNA arrays showed that 13 cancer-related genes were

upregulated > or = 2 fold and immunostaining results of the expression of the MET gene showed MET overexpression at the protein level, validating the cDNA arrays findings).

These references demonstrate that one of ordinary skill in the art would accept that it is more likely than not that gene amplification correlates with mRNA overexpression.

(2) mRNA Overexpression More Likely than not Correlates with Protein Overexpression

Numerous other references cited by Appellants demonstrate that mRNA overexpression more likely than not correlates with protein overexpression.[1] Indeed, in the Advisory Action mailed June 20, 2007, the Examiner expressly acknowledged that mRNA levels are predictive of polypeptide levels. Although there may not always be a 100% correlation between gene amplification and protein overexpression, the above discussed references evidence that gene amplification more likely than not correlates with mRNA overexpression and the Examiner acknowledges that mRNA overexpression more likely than not correlates with protein overexpression. Indeed, Appellants note the Board also expressly recognized the latter in Decision of the USPTO Board of Patent Appeals and Interferences, Appeal No. 2006-1469 at page 9. Hence, the utility of the present invention is not wholly inconsistent with the knowledge in the art. Thus, these references provide further evidence that one of ordinary skill in the art would believe that the claimed invention is supported by a specific, substantial, and credible utility.

g. The References Relied on by the Examiner do not Outweigh the Evidence Supporting Appellants' Asserted Utility

Throughout prosecution of the present application, Appellants have overcome numerous references relied on by the Examiner including references by Chen, Hu, Haynes, Gygi, Lian, Fessler, Greenbaum, Nagaraja, Waghray, Sagnaliev , Lilley, King, Bork, Madoz-Gurpide et al, and Sen. *See, e.g.,* Advisory Action mailed 6/20/07, Request for Continued Examination filed 8/17/07. In the final rejection, the Examiner relies on references by

[1] For example, the references by Wang, Munaut, Hui, Khal, Caberlotto, Misrachi and Shemesh, Stou, Gou and Xie, Van der Wilt, Grenback, Shen, and Fu, which were submitted with and are discussed in the Response and Request for Continued Examination filed 12/11/06, demonstrate that mRNA levels correlate well with protein expression levels.

Godbout, Li, Pennica, and Konopka, in an attempt to overcome Appellants' asserted utility. Appellants' respectfully disagree that these references make it more likely than not that one of ordinary skill in the art would reject Appellants' assertion of utility for the claimed PRO347 polypeptides based on amplification of the PRO347 nucleic acid.

(1) Godbout and Li are not Contrary to Appellants' Asserted Utility

The Examiner alleges Godbout teaches that "[t]he DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumours and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." Office action mailed 3/7/07, at page 8. Based on this statement in Godbout, the Office action argues that Appellants' assertion of utility is not sufficient because the specification does not teach that the protein encoded by the PRO347 gene would confer any selective advantage on a cell expressing it.

Appellants respectfully disagree that Godbout teaches that amplified genes are *only* overexpressed if they provide a selective advantage. Rather, Godbout, which focuses on *co-amplified* genes, states that "it is unlikely that a gene located ~ 400 kb from the *MYCN* gene will be consistently amplified as an intact unit unless its product provides a growth advantage to the cell." Page 21162 of Godbout. Thus, rather than conclude that an amplified gene must encode a polypeptide that provides a selective advantage, Godbout suggests that the selective advantage plays a role in why a particular gene may be co-amplified with another gene.

Appellants further respectfully submit that this aspect of the Godbout teachings is not relevant to Appellants' assertion of utility, which is not based on any gene that is alleged to be co-amplified. Indeed, amplification of PRO347 was confirmed by epicenter mapping. Specifically, Appellants confirmed that amplification of the closest known epicenter markers did not occur to a greater extent than that of PRO347. Appellants teach that this "strongly suggests that the DNAs tested are responsible for the

amplification of the particular region on the respective chromosome." Paragraph 0750. Thus, based on this teaching of the specification, one of ordinary skill in the art would conclude that PRO347 is not a co-amplified gene but rather an amplified gene.

Further, Appellants note that regardless of the co-amplification aspect of the Godbout reference, this reference teaches that a DEAD box gene, DDX1, shows good correlation between gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cancer cell lines studied. *See* pages 21164, 21167, and 21168. Thus, Godbout does not teach that Appellants' assertion of utility is wholly inconsistent with or violates any scientific principles nor does Godbout make it more likely than not that one of ordinary skill in the art would doubt Appellants' assertion of utility.

Li teaches that "genes that are concurrently amplified because of their location with respect to amplicons" generally do not show correlation between gene amplification and mRNA or polypeptide overexpression. However, just as Godbout is not persuasive evidence, Applicants respectfully disagree that Li is persuasive evidence in the context of the present invention. Framework and epicenter mapping analyses were carried out for PRO347 to confirm that PRO347, and not some other gene, is responsible for the observed gene amplification. This coupled with the high rates of observed amplification (approximately 2 to 8 fold amplification in nearly 70% of all tissues tested) indicates that PRO347 gene amplification more likely than not correlates with overexpression of the PRO347 polypeptide.

(2) Pennica and Konopka do not Overcome Appellants' Evidence Supporting Appellants' Asserted Utility

Appellants respectfully disagree with the Examiner's continued reliance on Pennica and Konopka to rejected the pending claims. Pennica does not demonstrate that *more likely than not* one of ordinary skill in the art would not expect gene amplification levels to correlate with protein overexpression. First, *WISP-1* gene amplification and RNA expression levels examined in Pennica showed a significant positive correlation. Second, although Pennica stated that *WISP-3* was not significantly amplified, it was amplified (P=1.666) and overexpressed. Third, although *WISP-2* gene amplification and RNA

expression levels seemed to be inversely related, Pennica suggests that this result might be inaccurate: "[b]ecause the center of the 20q13 amplicon has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon." *See* Pennica at 14722. Thus, because the RNA expression pattern of *WISP-2* cannot be accurately attributed to gene amplification of *WISP-2,* this result should be disregarded. Indeed, the teachings of Godbout taken with Pennica suggest that Pennica's conclusion that the observed amplification is not actually attributable to *WISP-2* is correct. Moreover, in the present case, appropriate controls for aneuploidy were used and page 137 of the present specification explains the procedures performed to confirm that the observed gene amplification was attributable in the present case to PRO347. Therefore, for this additional reason, Pennica *et al. does not make it more likely than not* that the present invention is not supported by a specific, substantial, and credible utility.

Appellants also disagree with the Examiner's reliance on Konopka *et al.* to establish that "[p]rotein expression is not related to gene amplification but to variation in the level of mRNA produced from a single genomic template." Appellants respectfully submit that the Examiner has generalized a very specific result disclosed by Konopka *et al.* to cover all genes. Konopka *et al.* actually state that "[p]rotein expression is not related to amplification of the ***abl*** gene but to variation in the level of *bcr-abl* mRNA produced from a single Ph^1 template." (See Konopka *et al.*, Abstract, emphasis added). The paper does not teach anything whatsoever about the correlation of protein expression and gene amplification in general, and provides no basis for the generalization that apparently underlies the present rejection. The statement of Konopka *et al.* that "[p]rotein expression is not related to amplification of the *abl* gene . . ." is not sufficient to establish lack of utility. It is not enough to show that for a particular gene a correlation does not exist. The law requires that the Examiner show evidence that it is more likely than not that such correlation, in general, does not exist. Such a showing has not been made.

Indeed, neither Pennica nor Konopka establishes that one of ordinary skill in the art would reject Appellants' asserted utility. Both of these references were overcome during prosecution of the '308 patent. Specifically, as explained above, the '308 is assigned to,

Genentech, Inc, who is the assignee of the present case. In the '308 patent, the inventors asserted the same diagnostic utility for the claimed polypeptide that Appellants assert, specifically a diagnostic utility based on gene amplification resulting in overexpression of the mRNA and subsequently, the protein of the gene. The examiner of the '308 patent repeatedly rejected but ultimately accepted that assertion of utility. In rejecting the assertion of utility, the examiner relied Pennica and Konopka but ultimately found these references overcome because the combined teachings of Pennica and Konopka are not directed towards the claimed polypeptide, nor towards genes in general, but rather are to a single gene or genes within a single family. Thus, their teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA or protein levels. For these same reasons, Pennica and Konopka do not support the present rejection of the claims pending in this application and are overcome.

For the reasons discussed above, Appellants respectfully maintain that the *totality* of this evidence currently under consideration demonstrates that it is more likely than not that one of ordinary skill in the art would accept Appellants' assertion of utility based on the principle that PRO347 is more likely than not overexpressed in lung or colon tumor tissues.

4. The Claimed Invention is Supported by a Utility that is Specific, Substantial, and Credible

Finally, use of the polypeptide sequence of PRO347 as a diagnostic marker is a specific, substantial, credible, and well established utility.

"Specific utility" is defined as:

> [a] utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a polynucleotide whose use is disclosed simply as a 'gene probe' or 'chromosome marker' would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

Revised Interim Utility Guidelines Training Materials, pgs. 5-6 (http://www.uspto.gov/web/offices/pac/utility/utilityguide.pdf). At pages 119 and 137 of the specification, the presently claimed polypeptides are asserted to be useful as targets for therapeutic intervention in lung or colon cancer or as diagnostic markers, indicating the presence of tumor cells in lung or colon tissue samples. These utilities are specific to the claimed polypeptides, which are encoded by nucleic acids that are amplified in lung or colon tumors.

"Substantial utility" is defined as:

> a utility that defines a 'real world' use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measure or further monitoring.

Revised Interim Utility Guidelines Training Materials, pg. 6 (http://www.uspto.gov/web/offices/pac/utility/utilityguide.pdf). The presently claimed polypeptides are also supported by a substantial utility because the utilities discussed above, *i.e.* therapeutic targets and diagnostic markers, are real world uses. For example, similar to the statement found in the above quote from the Guidelines, the present specification discloses an assay that measures gene amplification in cancerous cells. The patents, declarations and articles discussed above, *supra* at 12-37, correlate that gene amplification in cancerous cells with polypeptide overexpression in cancerous cells. Therefore, the claimed polypeptides are supported by a substantial utility.

"Credible" utility is defined as:

> Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being 'wrong'. Rather, Office personnel must determine if the assertion of utility is credible (*i.e.,* whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the

> assertion is seriously flawed, or (B the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A *credible* utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests.

Revised Interim Utility Guidelines Training Materials, pg. 5 (http://www.uspto.gov/web/offices/pac/utility/utilityguide.pdf). The present invention is supported by a credible utility. As discussed above, *supra* at 12-37, the patents, declarations, and references cited by Appellants demonstrate that the logic underlying Appellants assertion of utility is not seriously flawed, nor are the facts upon which utility is asserted inconsistent with the logic underlying the assertion of utility. Therefore, utilizing the claimed polypeptides as therapeutic targets or diagnostic markers in lung or colon cancer is a credible utility.

A "well established" utility is a:

> specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of the material, alone or taken with the knowledge of one skilled in the art.

Revised Interim Utility Guidelines Training Materials, pg. 7 (http://www.uspto.gov/web/offices/pac/utility/utilityguide.pdf). For the reasons demonstrated above, *supra* at 12-37, Appellants' asserted utility is specific, substantial, and credible. Hence, it is also well known.

For all the above reasons, Appellants have demonstrated currently pending claims 27-34 are supported by an asserted specific, substantial, credible and well-established utility and therefore, respectfully request that the rejection of claims 25-34 and 36 for lack of utility be reversed.

B. The Enablement Rejection Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

In the Final Office Action mailed July 10, 2008 and the Advisory Action mailed October 8, 2008, the Examiner maintains the rejection of claims 27-34 under 35 U.S.C. § 112, first paragraph, because it is alleged that the presently claimed invention is not supported by a substantial utility, and therefore, one skilled in the art would not know how to use the claimed invention. As discussed in the remarks above, Appellants respectfully submit that the claimed polypeptide is supported by a substantial utility. Accordingly, Appellants respectfully request reconsideration and reversal of the rejection of claims 27-34 under 35 U.S.C. § 112, first paragraph as allegedly not enabled because one of ordinary skill in the art allegedly would not know how to use the claimed PRO347 polypeptides.

X. CONCLUSION

For the reasons given above, Appellants submit that the specification discloses at least one patentable utility for the PRO347 polypeptides of claims 27-34, and that one of ordinary skill in the art would understand how to used the claimed polypeptides, for example in the diagnosis of lung and colon tumors. Therefore, claims 27-34 meet the requirements of 35 USC §101 and 35 USC §112, first paragraph. Accordingly, reversal of all the rejections of claims 58-65 and 68-70 is respectfully requested.

Respectfully submitted,

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CLAIMS APPENDIX

LISTING OF THE CLAIMS:

Claims 1-26 (canceled)

Claim 27 (previously presented): A polypeptide isolated from lung or colon tissue comprising:

(a) the amino acid sequence of the polypeptide shown in Figure 20 (SEQ ID NO:50);

(b) the amino acid sequence of the polypeptide shown in Figure 20 (SEQ ID NO:50), lacking its associated signal peptide;

(c) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 20 (SEQ ID NO:50);

(d) the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 20 (SEQ ID NO:50), lacking its associated signal peptide; or

(e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209532.

Claim 28 (previously presented): The polypeptide of claim 27 isolated from lung or colon tissue, comprising the amino acid sequence of the polypeptide shown in Figure 20 (SEQ ID NO:50).

Claim 29 (previously presented): The polypeptide of claim 27 isolated from lung or colon tissue, comprising the amino acid sequence of the polypeptide shown in Figure 20 (SEQ ID NO:50), lacking its associated signal peptide.

Claim 30 (previously presented): The polypeptide of claim 27 isolated from lung or colon tissue, comprising the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 20 (SEQ ID NO:50).

Claim 31 (previously presented): The polypeptide of claim 25 isolated from lung or colon tissue, comprising the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 20 (SEQ ID NO:50), lacking its associated signal peptide.

Claim 32 (previously presented): The polypeptide of claim 29 isolated from lung or colon tissue, comprising the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209532.

Claim 33 (previously presented): A chimeric polypeptide comprising a polypeptide according to claim 25 fused to a heterologous polypeptide.

Claim 34 (previously presented): The chimeric polypeptide of Claim 33, wherein said heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin.

Claim 35-36 (canceled)

EVIDENCE APPENDIX

Attached to this Appendix are the following declarations submitted under 37 C.F.R. §1.131, which the Examiner entered into the record on the dates indicated below:

1. Declaration of Audrey Goddard, Ph.D., entered June 26, 2003.
2. First Declaration of Paul Polakis, Ph.D., entered November 25, 2005.
3. Second Declaration of Paul Polakis, Ph.D., entered June 20, 2006.
4. Declaration of Randy Scott, Ph.D., entered December 11, 2006.
5. Declaration of Avi Ashkenazi, Ph.D., entered December 24, 2003.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Kevin P. Baker et al.	)	
	)	**Examiner: Kemmerer, E.**
Serial No. 09/944,396	)	
	)	**Group Art Unit No.: 1646**
Filing Date: August 30, 2001	)	
	)	
For SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME	)	

DECLARATION OF AUDREY D. GODDARD, Ph.D UNDER 37 C.F.R. § 1.132

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

I, Audrey D. Goddard, Ph.D. do hereby declare and say as follows:

1. I am a Senior Clinical Scientist at the Experimental Medicine/BioOncology, Medical Affairs Department of Genentech, Inc., South San Francisco, California 94080.

2. Between 1993 and 2001, I headed the DNA Sequencing Laboratory at the Molecular Biology Department of Genentech, Inc. During this time, my responsibilities included the identification and characterization of genes contributing to the oncogenic process, and determination of the chromosomal localization of novel genes.

3. My scientific Curriculum Vitae, including my list of publications, is attached to and forms part of this Declaration (Exhibit A).

4. I am familiar with a variety of techniques known in the art for detecting and quantifying the amplification of oncogenes in cancer, including the quantitative TaqMan PCR (i.e., "gene amplification") assay described in the above captioned patent application.

5. The TaqMan PCR assay is described, for example, in the following scientific publications: Higuchi *et al.*, Biotechnology 10:413-417 (1992) (Exhibit B); Livak *et al.*, PCR Methods Appl., 4:357-362 (1995) (Exhibit C) and Heid *et al.*, Genome Res. 6:986-994 (1996) (Exhibit D). Briefly, the assay is based on the principle that successful PCR yields a fluorescent signal due to Taq DNA polymerase-mediated exonuclease digestion of a fluorescently labeled oligonucleotide that is homologous to a sequence between two PCR primers. The extent of digestion depends directly on the amount of PCR, and can be quantified accurately by measuring the increment in fluorescence that results from decreased energy transfer. This is an extremely sensitive technique, which allows detection in the exponential phase of the PCR reaction and, as a result, leads to accurate determination of gene copy number.

6. The quantitative fluorescent TaqMan PCR assay has been extensively and successfully used to characterize genes involved in cancer development and progression. Amplification of protooncogenes has been studied in a variety of human tumors, and is widely considered as having etiological, diagnostic and prognostic significance. This use of the quantitative TaqMan PCR assay is exemplified by the following scientific publications: Pennica *et al.*, Proc. Natl. Acad. Sci. USA 95(25):14717-14722 (1998) (Exhibit E); Pitti *et al.*, Nature 396(6712):699-703 (1998) (Exhibit F) and Bieche *et al.*, Int. J. Cancer 78:661-666 (1998) (Exhibit G), the first two of which I am co-author. In particular, Pennica *et al.* have used the quantitative TaqMan PCR assay to study relative gene amplification of WISP and c-myc in various cell lines, colorectal tumors and normal mucosa. Pitti *et al.* studied the genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer, using the quantitative TaqMan PCR assay. Bieche *et al.* used the assay to study gene amplification in breast cancer.

7. It is my personal experience that the quantitative TaqMan PCR technique is technically sensitive enough to detect at least a 2-fold increase in gene copy number relative to control. It is further my considered scientific opinion that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

8. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Jan. 16, 2003
Date

Audrey Goddard
Audrey D. Goddard, Ph.D.

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PROFESSIONAL EXPERIENCE

1993-present

Genentech, Inc.
South San Francisco, CA

2001 - present **Senior Clinical Scientist**
Experimental Medicine / BioOncology, Medical Affairs

Responsibilities:
- *Companion diagnostic oncology products*
- *Acquisition of clinical samples from Genentech's clinical trials for translational research*
- *Translational research using clinical specimen and data for drug development and diagnostics*
- *Member of Development Science Review Committee, Diagnostic Oversight Team, 21 CFR Part 11 Subteam*

Interests:
- *Ethical and legal implications of experiments with clinical specimens and data*
- *Application of pharmacogenomics in clinical trials*

1998 - 2001 **Senior Scientist**
Head of the DNA Sequencing Laboratory, Molecular Biology Department, Research

Responsibilities:
- *Management of a laboratory of up to nineteen –including postdoctoral fellow, associate scientist, senior research associate and research assistants/associate levels*
- *Management of a $750K budget*
- *DNA sequencing core facility supporting a 350+ person research facility.*
- *DNA sequencing for high throughput gene discovery, - ESTs, cDNAs, and constructs*
- *Genomic sequence analysis and gene identification*
- *DNA sequence and primary protein analysis*

Research:
- *Chromosomal localization of novel genes*
- *Identification and characterization of genes contributing to the oncogenic process*
- *Identification and characterization of genes contributing to inflammatory diseases*
- *Design and development of schemes for high throughput genomic DNA sequence analysis*
- *Candidate gene prediction and evaluation*

1993 - 1998 Scientist
Head of the DNA Sequencing Laboratory, Molecular Biology Department, Research

Responsibilities
- *DNA sequencing core facility supporting a 350+ person research facility*
- *Assumed responsibility for a pre-existing team of five technicians and expanded the group into fifteen, introducing a level of middle management and additional areas of research*
- *Participated in the development of the basic plan for high throughput secreted protein discovery program – sequencing strategies, data analysis and tracking, database design*
- *High throughput EST and cDNA sequencing for new gene identification.*
- *Design and implementation of analysis tools required for high throughput gene identification.*
- *Chromosomal localization of genes encoding novel secreted proteins.*

Research:
- *Genomic sequence scanning for new gene discovery.*
- *Development of signal peptide selection methods.*
- *Evaluation of candidate disease genes.*
- *Growth hormone receptor gene SNPs in children with idiopathic short stature*

Imperial Cancer Research Fund **1989-1992**
London, UK with Dr. Ellen Solomon

6/89 –12/92 Postdoctoral Fellow
- Cloning and characterization of the genes fused at the acute promyelocytic leukemia translocation breakpoints on chromosomes 17 and 15.
- Prepared a successfully funded European Union multi-center grant application

McMaster University **1983**
Hamilton, Ontario, Canada with Dr. G. D. Sweeney

5/83 – 8/83: NSERC Summer Student
- *In vitro* metabolism of β-naphthoflavone in C57Bl/6J and DBA mice

EDUCATION

Ph.D. "Phenotypic and genotypic effects of mutations in the human retinoblastoma gene." **Supervisor:** Dr. R. A. Phillips	University of Toronto Toronto, Ontario, Canada. Department of Medical Biophysics.	1989
Honours B.Sc "The *in vitro* metabolism of the cytochrome P-448 inducer β-naphthoflavone in C57BL/6J mice." **Supervisor:** Dr. G. D. Sweeney	McMaster University, Hamilton, Ontario, Canada. Department of Biochemistry	1983

ACADEMIC AWARDS

Imperial Cancer Research Fund Postdoctoral Fellowship	1989-1992
Medical Research Council Studentship	1983-1988
NSERC Undergraduate Summer Research Award	1983
Society of Chemical Industry Merit Award (Hons. Biochem.)	1983
Dr. Harry Lyman Hooker Schnlarship	1981-1983
J.L.W. Gill Scholarship	1981-1982
Business and Professional Women's Club Scholarship	1980-1981
Wyerhauser Foundation Scholarship	1979-1980

INVITED PRESENTATIONS

Genentech's gene discovery pipeline: High throughput identification, cloning and characterization of novel genes. Functional Genomics: From Genome to Function. Litchfield Park, AZ., USA. October 2000

High throughput identification, cloning and characterization of novel genes. G2K:Back to Science, Advances in Genome Biology and Technology I. Marco Island, FL, USA. February 2000

Quality control in DNA Sequencing: The use of Phred and Phrap. Bay Area Sequencing Users Meeting, Berkeley, CA, USA. April 1999

High throughput secreted protein identification and cloning. Tenth International Genome Sequencing and Analysis Conference, Miami, FL, USA. September 1998

The evolution of DNA sequencing: The Genentech perspective. Bay Area Sequencing Users Meeting, Berkeley, CA. USA. May 1998

Partial Growth Hormone Insensitivity: The role of GH-receptor mutations in Idiopathic Short Stature. Tenth Annual National Cooperative Growth Study Investigators Meeting, San Francisco, CA, USA. October, 1996

Growth hormone (GH) receptor defects are present in selected children with non-GH-deficient short stature: A molecular basis for partial GH-insensitivity. 76th Annual Meeting of The Endocrine Society, Anaheim, CA, USA. June 1994

A previously uncharacterized gene, myl, is fused to the retinoic acid receptor alpha gene in acute promyelocytic leukemia. XV International Association for Comparative Research on Leukemia and Related Disease, Padua, Italy. October 1991

PATENTS

Goddard A, Godowski PJ, Gurney AL. NL2 Tie ligand homologue polypeptide. Patent Number: 6,455,496. Date of Patent: Sept. 24, 2002.

Goddard A, Godowski PJ and Gurney AL. NL3 Tie ligand homolngue nucleic acids. Patent Number: 6,426,218. Date of Patent: July 30, 2002.

Godowski P, Gurney A, Hillan KJ, Botstein D, **Goddard A**, Roy M, Ferrara N, Tumas D, Schwall R. NL4 Tie ligand homologue nucleic acid. Patent Number: 5,4137,770. Date of Patent: July 2, 2002.

Ashkenazi A, Fong S, **Goddard A**, Gurney AL, Napier MA, Tumas D, Wood WI. Nucleic acid encoding A-33 related antigen poly peptides. Patent Number: 6,410,708. Date of Patent:: Jun. 25, 2002.

Botstein DA, Cohen RL, **Goddard AD**, Gurney AL, Hillan KJ, Lawrence DA, Levine AJ, Pennica D, Roy MA and Wood WI. WISP polypeptides and nucleic acids encoding same. Patent Number: 6,387,657. Date of Patent: May 14, 2002.

Goddard A, Godowski PJ and Gurney AL. Tie ligands. Patent Number: 6,372,491. Date of Patent: April 16, 2002.

Godowski PJ, Gurney AL, **Goddard A** and Hillan K. TIE ligand homolngue antibody. Patent Number: 6,350,450. Date of Patent: Feb. 26, 2002.

Fong S, Ferrara N, **Goddard** A, Godowski PJ, Gurney AL, Hillan K and Williams PM. Tie receptor tyrosine kinase ligand homologues. Patent Number: 6,348,351. Date of Patent: Feb. 10, 2002.

Goddard A, Godowski PJ and Gurney AL. Ligand homologues. Patent Number: 6,348,350. Date of Patent: Feb. 19, 2002.

Attie KM, Carlsson LMS, Gesundheit N and **Goddard A**. Treatment of partial growth hormone insensitivity syndrome. Patent Number: 6,207,640. Date of Patent: March 27, 2001.

Fong S, Ferrara N, **Goddard A**, Godowski PJ, Gurney AL, Hillan K and Williams PM. Nucleic acids encoding NL-3. Patent Number: 6,074,873. Date of Patent: June 13, 2000

Attie K, Carlsson LMS, Gesunheit N and **Goddard A**. Treatment of partial growth hormone insensitivity syndrome. Patent Number: 5,824,642. Date of Patent: October 20, 1998

Attie K, Carlsson LMS, Gesunheit N and **Goddard A**. Treatment of partial growth hormone insensitivity syndrome. Patent Number: 5,646,113. Date of Patent: July 8, 1997

Multiple additional provisional applications filed

PUBLICATIONS

Seshasayee D, Dowd P, Gu Q, Erickson S, **Goddard AD** Comparative sequence analysis of the *HER2* locus in mouse and man. Manuscript in preparation.

Abuzzahab MJ, **Goddard A**, Grigorescu F, Lautier C, Smith RJ and Chernausek SD. Human IGF-1 receptor mutations resulting in pre- and post-natal growth retardation. Manuscript in preparation.

Aggarwal S, Xie, M-H, Foster J, Frantz G, Stinson J, Corpuz RT, Simmons L, Hillan K, Yansura DG, Vandlen RL, **Goddard AD** and Gurney AL. FHFR, a novel receptor for the fibroblast growth factors. Manuscript submitted.

Adams SH, Chui C, Schilbach SL, Yu XX, **Goddard AD**, Grimaldi JC, Lee J, Dowd P, Colman S., Lewin DA. (2001) BFIT, a unique acyl-CoA thioesterase induced in thermogenic brown adipose tissue: Cloning, organization of the human gene, and assessment of a potential link to obesity. *Biochemical Journal* **360**: 135-142.

Lee J, Ho WH, Maruoka M, Corpuz RT, Baldwin DT, Foster JS, **Goddard AD**, Yansura DG, Vandlen RL, Wood WI, Gurney AL. (2001) IL-17E, a novel proinflammatory ligand for the IL-17 receptor homolog IL-17Rh1. *Journal of Biological Chemistry* **276**(2): 1660-1664.

Xie M-H, Aggarwal S, Ho W-H, Foster J, Zhang Z, Stinson J, Wood WI, **Goddard AD** and Gurney AL. (2000) Interleukin (IL)-22, a novel human cytokine that signals through the interferon-receptor related proteins CRF2-4 and IL-22R. *Journal of Biological Chemistry* **275**: 31335-31339.

Weiss GA, Watanabe CK, Zhong A, **Goddard A** and Sidhu SS. (2000) Rapid mapping of protein functional epitopes by combinatorial alanine scanning. *Proc. Natl. Acad. Sci. USA* **97**: 8050-8054.

Guo S, Yamaguchi Y, Schilbach S, Wada T, Lee J, **Goddard A**, French D , Handa H, Rosenthal A. (2000) A regulator of transcriptional elongation controls vertebrate neuronal development. *Nature* **408**: 366-369.

Yan M, Wang L-C, Hymowitz SG, Schilbach S, Lee J, **Goddard A**, de Vos AM, Gao WQ, Dixit VM. (2000) Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. *Science* **290**: 523-527.

Sehl PD, Tai JTN, Hillan KJ, Brown LA, **Goddard A**, Yang R, Jin H and Lowe DG. (2000) Application of cDNA microarrays in determining molecular phenotype in cardiac growth, development, and response to injury. *Circulation* **101**: 1990-1999.

Guo S, Brush J, Teraoka H, **Goddard A**, Wilson SW, Mullins MC and Rosenthal A. (1999) Development of noradrenergic neurons in the zebrafish hindbrain requires BMP, FGF8, and the homeodomain protein soulless/Phox2A. *Neuron* **24**: 555-566.

Stone D, Murone, M, Luoh, S, Ye W, Armanini P, Gurney A, Phillips HS, Brush, J, **Goddard A**, de Sauvage FJ and Rosenthal A. (1999) Characterization of the human suppressor of fused: a negative regulator of the zinc-finger transcription factor Gli. *J. Cell Sci.* **112**: 4437-4448.

Xie M-H, Holcomb I, Deuel B, Dowd P, Huang A, Vagts A, Foster J, Liang J, Brush J, Gu Q, Hillan K, **Goddard A** and Gurney, A.L. (1999) FGF-19, a novel fibroblast growth factor with unique specificity for FGFR4. *Cytokine* **11**: 729-735.

Yan M, Lee J, Schilbach S, **Goddard A** and Dixit V. (1999) mE10, a novel caspase recruitment domain-containing proapoptotic molecule. *J. Biol. Chem.* 274(15): 10287-10292.

Gurney AL, Marsters SA, Huang RM, Pitti RM, Mark DT, Baldwin DT, Gray AM, Dowd P, Brush J, Heldens S, Schow P, **Goddard AD**, Wood WI, Baker KP, Godowski PJ and Ashkenazi A. (1999) Identification of a new member of the tumor necrosis factor family and its receptor, a human ortholog of mouse GITR. *Current Biology* 9(4): 215-218.

Ridgway JBB, Ng E, Kern JA ,Lee J, Brush J, **Goddard A** and Carter P. (1999) Identification of a human anti-CD55 single-chain Fv by subtractive panning of a phage library using tumor and nontumor cell lines. *Cancer Research* 59: 2718-2723.

Pitti RM, Marsters SA, Lawrence DA, Roy M, Kischkel FC, Dowd P, Huang A, Donahue CJ, Sherwood SW, Baldwin DT, Godowski PJ, Wood WI, Gurney AL, Hillan KJ, Cohen RL, **Goddard AD**, Botstein D and Ashkenazi A. (1998) Genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer. *Nature* 396(6712): 699-703.

Pennica D, Swanson TA, Welsh JW, Roy MA, Lawrence DA, Lee J, Brush J, Taneyhill LA, Deuel B, Lew M, Watanabe C, Cohen RL, Melhem MF, Finley GG, Quirke P, **Goddard AD**, Hillan KJ, Gurney AL, Botstein D and Levine AJ. (1998) WISP genes are members of the connective tissue growth factor family that are up-regulated in wnt-1-transformed cells and aberrantly expressed in human colon tumors. *Proc. Natl. Acad. Sci. USA.* 95(25): 14717-14722.

Yang RB, Mark MR, Gray A, Huang A, Xie MH, Zhang M, **Goddard A**, Wood WI, Gurney AL and Godowski PJ. (1998) Toll-like receptor-2 mediates lipopolysaccharide-induced cellular signalling. *Nature* 395(6699): 284-288.

Merchant AM, Zhu Z, Yuan JQ, **Goddard A**, Adams CW, Presta LG and Carter P. (1998) An efficient route to human bispecific IgG. *Nature Biotechnology* 16(7): 677-681.

Marsters SA, Sheridan JP, Pitti RM, Brush J, **Goddard A** and Ashkenazi A. (1998) Identification of a ligand for the death-domain-containing receptor Apo3. *Current Biology* 8(9): 525-528.

Xie J, Murone M, Luoh SM, Ryan A, Gu Q, Zhang C, Bonifas JM, Lam CW, Hynes M, **Goddard A**, Rosenthal A, Epstein EH Jr. and de Sauvage FJ. (1998) Activating Smoothened mutations in sporadic basal-cell carcinoma. *Nature*. 391(6662): 90-92.

Marsters SA, Sheridan JP, Pitti RM, Huang A, Skubatch M, Baldwin D, Yuan J, Gurney A, **Goddard AD**, Godowski P and Ashkenazi A. (1997) A novel receptor for Apo2L/TRAIL contains a truncated death domain. *Current Biology*. 7(12): 1003-1006.

Hynes M, Stone DM, Dowd M, Pitts-Meek S, **Goddard A**, Gurney A and Rosenthal A. (1997) Control of cell pattern in the neural tube by the zinc finger transcription factor *Gli-1*. *Neuron* 19: 15–26.

Sheridan JP, Marsters SA, Pitti RM, Gurney A., Skubatch M, Baldwin D, Ramakrishnan L, Gray CL, Baker K, Wood WI, **Goddard AD**, Godowski P, and Ashkenazi A. (1997) Control of TRAIL-Induced Apoptosis by a Family of Signaling and Decoy Receptors. *Science* 277 (5327): 818-821.

Goddard AD, Dowd P, Chernausek S, Geffner M, Gertner J, Hintz R, Hopwood N, Kaplan S, Plotnick L, Rogol A, Rosenfield R, Saenger P, Mauras N, Hershkopf R, Angulo M and Attie, K. (1997) Partial growth hormone insensitivity: The role of growth hormone receptor mutations in idiopathic short stature. *J. Pediatr.* 131: S51-55.

Klein RD, Sherman D, Ho WH, Stone D, Bennett GL, Moffat B, Vandlen R, Simmons L, Gu Q, Hongo JA, Devaux B, Poulsen K, Armanini M, Nozaki C, Asai N, **Goddard A**, Phillips H, Henderson CE, Takahashi M and Rosenthal A. (1997) A GPI-linked protein that interacts with Ret to form a candidate neurturin receptor. *Nature*. 387(6634): 717-21.

Stone DM, Hynes M, Armanini M, Swanson TA, Gu Q, Johnson RL, Scott MP, Pennica D, **Goddard A**, Phillips H, Noll M, Hooper JE, de Sauvage F and Rosenthal A. (1996) The tumour-suppressor gene patched encodes a candidate receptor for Sonic hedgehog. *Nature* 384(6605): 129-34.

Marsters SA, Sheridan JP, Donahue CJ, Pitti RM, Gray CL, **Goddard AD**, Bauer KD and Ashkenazi A. (1996) Apo-3, a new member of the tumor necrosis factor receptor family, contains a death domain and activates apoptosis and NF-kappa β. *Current Biology* 6(12): 1669-76.

Rothe M, Xiong J, Shu HB, Williamson K, **Goddard A** and Goeddel DV. (1996) I-TRAF is a novel TRAF-interacting protein that regulates TRAF-mediated signal transduction. *Proc. Natl. Acad. Sci. USA* 93: 8241-8246.

Yang M, Luoh SM, **Goddard A**, Reilly D, Henzel W and Bass S. (1996) The bglX gene located at 47.8 min on the Escherichia coli chromosome encodes a periplasmic beta-glucosidase. *Microbiology* 142: 1659-65.

Goddard AD and Black DM. (1996) Familial Cancer In Molecular Endocrinology of Cancer. Waxman, J. Ed. Cambridge University Press, Cambridge UK, pp.187-215.

Treanor JJS, Goodman L, de Sauvage F, Stone DM, Poulson KT, Beck CD, Gray C, Armanini MP, Pollocks RA, Hefti F, Phillips HS, **Goddard A**, Moore MW, Buj-Bello A, Davis AM, Asai N, Takahashi M, Vandlen R, Henderson CE and Rosenthal A. (1996) Characterization of a receptor for GDNF. *Nature* 382: 80-83.

Klein RD, Gu Q, **Goddard A** and Rosenthal A. (1996) Selection for genes encoding secreted proteins and receptors. *Proc. Natl. Acad. Sci. USA* 93: 7108-7113.

Winslow JW, Moran P, Valverde J, Shih A, Yuan JQ, Wong SC, Tsai SP, **Goddard A**, Henzel WJ, Hefti F and Caras I. (1995) Cloning of AL-1, a ligand for an Eph-related tyrosine kinase receptor involved in axon bundle formation. *Neuron* 14: 973-981.

Bennett BD, Zeigler FC, Gu Q, Fendly B, **Goddard AD**, Gillett N and Matthews W. (1995) Molecular cloning of a ligand for the EPH-related receptor protein-tyrosine kinase Htk. *Proc. Natl. Acad. Sci. USA* 92: 1866-1870.

Huang X, Yuang J, **Goddard A**, Foulis A, James RF, Lernmark A, Pujol-Borrell R, Rabinovitch A, Somoza N and Stewart TA. (1995) Interferon expression in the pancreases of patients with type I diabetes. *Diabetes* 44: 658-664.

Goddard AD, Yuan JQ, Fairbairn L, Dexter M, Borrow J, Kozak C and Solomon E. (1995) Cloning of the murine homolog of the leukemia-associated PML gene. *Mammalian Genome* 6: 732-737.

Goddard AD, Covello R, Luoh SM, Clackson T, Attie KM, Gesundheit N, Rundle AC, Wells JA, Carlsson LMTI and The Growth Hormone Insensitivity Study Group. (1995) Mutations of the growth hormone receptor in children with idiopathic short stature. *N. Engl. J. Med.* **333**: 1093-1098.

Kuo SS, Moran P, Gripp J, Armanini M, Phillips HS, **Goddard A** and Caras IW. (1994) Identification and characterization of Batk, a predominantly brain-specific non-receptor protein tyrosine kinase related to Csk. *J. Neurosci. Res.* **38**: 705-715.

Mark MR, Scadden DT, Wang Z, Gu Q, **Goddard A** and Godowski PJ. (1994) Rse, a novel receptor-type tyrosine kinase with homology to Axl/Ufo, is expressed at high levels in the brain. *Journal of Biological Chemistry* **269**: 10720-10728.

Borrow J, Shipley J, Howe K, Kiely F, **Goddard A**, Sheer D, Srivastava A, Antony AC, Fioretos T, Mitelman F and Solomon E. (1994) Molecular analysis of simple variant translocations in acute promyelocytic leukemia. *Genes Chromosomes Cancer* **9**: 234-243.

Goddard AD and Solomon E. (1993) Genetics of Cancer. *Adv. Hum. Genet.* **21**: 321-376.

Borrow J, **Goddard AD**, Gibbons B, Katz F, Swirsky D, Floretos T, Dube I, Winfield DA, Kingston J, Hagemeijer A, Rees JKH, Lister AT and Solomon E. (1992) Diagnosis of acute promyelocytic leukemia by RT-PCR: Detection of *PML-RARA* and *RARA-PML* fusion transcripts. *Br. J. Haematol.* **82**: 529-540.

Goddard AD, Borrow J and Solomon E. (1992) A previously uncharacterized gene, PML, is fused to the retinoic acid receptor alpha gene in acute promyelocytic leukemia. *Leukemia* **6 Suppl 3**: 117S–119S.

Zhu X, Dunn JM, **Goddard AD**, Squire JA, Becker A, Phillips RA and Gallie BL. (1992) Mechanisms of loss of heterozygosity in retinoblastoma. *Cytogenet. Cell. Genet.* **59**: 248-252.

Foulkes W, **Goddard A.** and Patel K. (1991) Retinoblastoma linked with Seascale [letter]. *British Med. J.* **302**: 409.

Goddard AD, Borrow J, Freemont PS and Solomon E. (1991) Characterization of a novel zinc finger gene disrupted by the t(15;17) in acute promyelocytic leukemia. *Science* **254**: 1371-1374.

Solomon E, Borrow J and **Goddard AD**. (1991) Chromosomal aberrations in cancer. *Science* **254**: 1153-1160.

Pajunen L, Jones TA, **Goddard A**, Sheer D, Solomon E, Pihlajaniemi T and Kivirikko KI. (1991) Regional assignment of the human gene coding for a multifunctional peptide (P4HB) acting as the β–subunit of prolyl-4-hydroxylase and the enzyme protein disulfide isomerase to 17q25. *Cytogenet. Cell. Genet.* **56**: 165-168.

Borrow J, Black DM, **Goddard AD**, Yagle MK, Frischauf A.-M and Solomon E. (1991) Construction and regional localization of a *Not*I linking library from human chromosome 17q. *Genomics* **10**: 477–480.

Borrow J, **Goddard AD**, Sheer D and Solomon E. (1990) Molecular analysis of acute promyelocytic leukemia breakpoint cluster region on chromosome 17. *Science* **249**: 1577-1580.

Myers JC, Jones TA, Pohjolainen E-R, Kadri AS, **Goddard AD**, Sheer D, Solomon E and Pihlajaniemi T. (1990) Molecular cloning of 5(IV) collagen and assignment of the gene to the region of the region of the X-chromosome containing the Alport Syndrome locus. *Am. J. Hum. Genet.* 46: 1024-1033.

Gallie BL, Squire JA, **Goddard A**, Dunn JM, Canton M, Hinton D, Zhu X and Phillips RA. (1990) Mechanisms of oncogenesis in retinoblastoma. *Lab. Invest.* 62: 394-408.

Goddard AD, Phillips RA, Greger V, Passarge E, Hopping W, Gallie BL and Horsthemke B. (1990) Use of the RB1 cDNA as a diagnostic probe in retinoblastoma families. *Clinical Genetics* 37: 117-126.

Zhu XP, Dunn JM, Phillips RA, **Goddard AD**, Paton KE, Becker A and Gallie BL. (1989) Germline, but not somatic, mutations of the RB1 gene preferentially involve the paternal allele. *Nature* 340: 312-314.

Gallie BL, Dunn JM, **Goddard A**, Becker A and Phillips RA. (1986) Identification of mutations in the putative retinoblastoma gene. In Molecular Biology of The Eye: Genes, Vision and Ocular Disease. UCLA Symposia on Molecular and Cellular Biology, New Series, Volume 88. J. Piatigorsky, T. Shinohara and P.S. Zelenka, Eds. Alan R. Liss, Inc., New York, 1988, pp. 427-436.

Goddard AD, Balakier H, Canton M, Dunn J, Squire J, Reyes E, Becker A, Phillips RA and Gallie BL. (1988) Infrequent genomic rearrangement and normal expression of the putative RB1 gene in retinoblastoma tumors. *Mol. Cell. Biol.* 8: 2082-2088.

Squire J, Dunn J, **Goddard A**, Hoffman T, Musarella M, Willard HF, Becker AJ, Gallie BL and Phillips RA. (1986) Cloning of the esterase D gene: A polymorphic gene probe closely linked to the retinoblastoma locus on chromosome 13. *Proc. Natl. Acad. Sci.* USA 83: 6573-6577.

Squire J, **Goddard AD**, Canton M, Becker A, Phillips RA and Gallie BL (1986) Tumour induction by the retinoblastoma mutation is independent of N-*myc* expression. *Nature* 322: 555-557.

Goddard AD, Heddle JA, Gallie BL and Phillips RA. (1985) Radiation sensitivity of fibroblasts of bilateral retinoblastoma patients as determined by micronucleus induction *in vitro*. *Mutation Research* 152: 31-38.

DECLARATION OF PAUL POLAKIS, Ph.D.

I, Paul Polakis, Ph.D., declare and say as follows:

1. I was awarded a Ph.D. by the Department of Biochemistry of the Michigan State University in 1984. My scientific Curriculum Vitae is attached to and forms part of this Declaration (Exhibit A).

2. I am currently employed by Genentech, Inc. where my job title is Staff Scientist. Since joining Genentech in 1999, one of my primary responsibilities has been leading Genentech's Tumor Antigen Project, which is a large research project with a primary focus on identifying tumor cell markers that find use as targets for both the diagnosis and treatment of cancer in humans.

3. As part of the Tumor Antigen Project, my laboratory has been analyzing differential expression of various genes in tumor cells relative to normal cells. The purpose of this research is to identify proteins that are abundantly expressed on certain tumor cells and that are either (i) not expressed, or (ii) expressed at lower levels, on corresponding normal cells. We call such differentially expressed proteins "tumor antigen proteins". When such a tumor antigen protein is identified, one can produce an antibody that recognizes and binds to that protein. Such an antibody finds use in the diagnosis of human cancer and may ultimately serve as an effective therapeutic in the treatment of human cancer.

4. In the course of the research conducted by Genentech's Tumor Antigen Project, we have employed a variety of scientific techniques for detecting and studying differential gene expression in human tumor cells relative to normal cells, at genomic DNA, mRNA and protein levels. An important example of one such technique is the well known and widely used technique of microarray analysis which has proven to be extremely useful for the identification of mRNA molecules that are differentially expressed in one tissue or cell type relative to another. In the course of our research using microarray analysis, we have identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, we have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. We have then compared the levels of mRNA and protein in both the tumor and normal cells analyzed.

5. From the mRNA and protein expression analyses described in paragraph 4 above, we have observed that there is a strong correlation between changes in the level of mRNA present in any particular cell type and the level of protein

expressed from that mRNA in that cell type. In approximately 80% of our observations we have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells.

6. Based upon my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. While there have been published reports of genes for which such a correlation does not exist, it is my opinion that such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 5/07/04

By: Paul Polakis

Paul Polakis, Ph.D.

SV 2031808 v1

CURRICULUM VITAE

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EDUCATION:

Ph.D., Biochemistry, Department of Biochemistry,
Michigan State University (1984)

B.S., Biology. College of Natural Science, Michigan State University (1977)

PROFESSIONAL EXPERIENCE:

2002-present	Staff Scientist, Genentech, Inc S. San Francisco, CA
1999- 2002	Senior Scientist, Genentech, Inc., S. San Francisco, CA
1997 -1999	Research Director Onyx Pharmaceuticals, Richmond, CA
1992- 1996	Senior Scientist, Project Leader, Onyx Pharmaceuticals, Richmond, CA
1991-1992	Senior Scientist, Chiron Corporation, Emeryville, CA.
1989-1991	Scientist, Cetus Corporation, Emeryville CA.
1987-1989	Postdoctoral Research Associate, Genentech, Inc., South SanFrancisco, CA.
1985-1987	Postdoctoral Research Associate, Department of Medicine, Duke University Medical Center, Durham, NC

1984-1985	Assistant Professor, Depar. ;nt of Chemistry, Oberlin College, Oberlin, Ohio
1980-1984	Graduate Research Assistant, Department of Biochemistry, Michigan State University East Lansing, Michigan

PUBLICATIONS:

1. **Polakis, P G.** and Wilson, J. E. 1982 Purification of a Highly Bindable Rat Brain Hexokinase by High Performance Liquid Chromatography. **Biochem. Biophys. Res. Commun.** 107, 937-943.

2. **Polakis, P.G.** and Wilson, J. E. 1984 Proteolytic Dissection of Rat Brain Hexokinase: Determination of the Cleavage Pattern during Limited Digestion with Trypsin. **Arch. Biochem. Biophys.** 234, 341-352.

3. **Polakis, P. G.** and Wilson, J. E. 1985 An Intact Hydrophobic N-Terminal Sequence is Required for the Binding Rat Brain Hexokinase to Mitochondria. **Arch. Biochem. Biophys.** 236, 328-337.

4. Uhing, R.J., **Polakis,P.G.** and Snyderman, R. 1987 Isolaton of GTP-binding Proteins from Myeloid HL60 Cells. **J. Biol. Chem.** 262, 15575-15579.

5. **Polakis, P.G.**, Uhing, R.J. and Snyderman, R. 1988 The Formylpeptide Chemoattractant Receptor Copurifies with a GTP-binding Protein Containing a Distinct 40 kDa Pertussis Toxin Substrate. **J. Biol. Chem.** 263, 4969-4979.

6. Uhing, R. J., Dillon, S., **Polakis, P. G.**, Truett, A. P. and Snyderman, R. 1988 Chemoattractant Receptors and Signal Transduction Processes in Cellular and Molecular Aspects of Inflammation (Poste, G. and Crooke, S. T. eds.) pp 335-379.

7. **Polakis, P.G.**, Evans, T. and Snyderman 1989 Multiple Chromatographic Forms of the Formylpeptide Chemoattractant Receptor and their Relationship to GTP-binding Proteins. **Biochem. Biophys. Res. Commun.** 161, 276-283.

8. **Polakis, P. G.**, Snyderman, R. and Evans, T. 1989 Characterization of G25K, a GTP-binding Protein Containing a Novel Putative Nucleotide Binding Domain. **Biochem. Biophys. Res. Comun.** 160, 25-32.

9. **Polakis, P.**, Weber,R.F., Nevins,B., Didsbury, J. Evans,T. and Snyderman, R. 1989 Identification of the ral and rac1 Gene Products, Low Molecular Mass GTP-binding Proteins from Human Platelets. **J. Biol. Chem.** 264, 16383-16389.

10. Snyderman, R., Perianin, A., Evans, T., **Polakis, P.** and Didsbury, J. 1989 G Proteins and Neutrophil Function. In ADP-Ribosylating Toxins and G Proteins: Insights into Signal Transduction. (J. Moss and M. Vaughn, eds.) Amer. Soc. Microbiol. pp. 295-323.

11. Hart, M.J., **Polakis, P.G.**, Evans, T. and Cerrione, R.A. 1990 Identification and Charaterization of an Epidermal Growth Factor-Stimulated Phosphorylation of a Specific Low Molecular Mass GTP-binding Protein in a Reconstituted Phospholipid Vesicle System. **J. Biol. Chem.** 265, 5990-6001.

12. Yatani, A., Okabe, K., **Polakis, P.** Halenbeck, R. McCormick, F. and Brown, A. M. 1990 ras p21 and GAP Inhibit Coupling of Muscarinic Receptors to Atrial K^+ Channels. **Cell.** 61, 769-776.

13. Munemitsu, S., Innis, M.A., Clark, R., McCormick, F., Ullrich, A. and **Polakis, P.G.** 1990 Molecular Cloning and Expression of a G25K cDNA, the Human Homolog of the Yeast Cell Cycle Gene CDC42. **Mol. Cell. Biol.** 10, 5977-5982.

14. Polakis, P.G. Rubinfeld, B. Evans, T. and McCormick, F. 1991 Purification of Plasma Membrane-Associated GTPase Activating Protein (GAP) Specific for rap-1/krev-1 from HL60 Cells. **Proc. Natl. Acad. Sci. USA** 88, 239-243.

15. Moran, M. F., **Polakis, P.**, McCormick, F., Pawson, T. and Ellis, C. 1991 Protein Tyrosine Kinases Regulate the Phosphorylation, Protein Interactions, Subcellular Distribution, and Activity of p21ras GTPase Activating Protein. **Mol. Cell. Biol.** 11, 1804-1812

16. Rubinfeld, B., Wong, G., Bekesi, E. Wood, A. McCormick, F. and **Polakis, P. G.** 1991 A Synthetic Peptide Corresponding to a Sequence in the GTPase Activating Protein Inhibits $p21^{ras}$ Stimulation and Promotes Guanine Nucleotide Exchange. **Internatl. J. Peptide and Prot. Res.** 38, 47-53.

17. Rubinfeld, B., Munemitsu, S., Clark, R., Conroy, L., Watt, K., Crosier, W., McCormick, F., and **Polakis, P.** 1991 Molecular Cloning of a GTPase Activating Protein Specific for the Krev-1 Protein $p21^{rap1}$. **Cell** 65, 1033-1042.

18. Zhang, K. Papageorge, A., G., Martin, P., Vass, W. C., Olah, Z., **Polakis, P.**, McCormick, F. and Lowy, D, R. 1991 Heterogenous Amino Acids in RAS and Rap1A Specifying Sensitivity to GAP Proteins. **Science** 254, 1630-1634.

19. Martin, G., Yatani, A., Clark, R., **Polakis, P.**, Brown, A. M. and McCormick, F. 1992 GAP Domains Responsible for $p21^{ras}$-dependent Inhibition of Muscarinic Atrial K^+ Channel Currents. **Science** 255, 192-194.

20. McCormick, F., Martin, G. A., Clark, R., Bollag, G. and **Polakis, P** . 1992 Regulation of p21ras by GTPase Activating Proteins. Cold Spring Harbor **Symposia on Quantitative Biology**. Vol. 56, 237-241.

21. Pronk, G. B., **Polakis, P.**, Wong, G., deVries-Smits, A. M., Bos J. L. and McCormick, F. 1992 $p60^{v\text{-}src}$ Can Associate with and Phosphorylate the $p21^{ras}$ GTPase Activating Protein. **Oncogene** 7,389-394.

22. Polakis P. and McCormick, F. 1992 Interactions Between $p21^{ras}$ Proteins and Their GTPase Activating Proteins. In **Cancer Surveys** (Franks, L. M., ed.) 12, 25-42.

23. Wong, G., Muller, O., (k, R., Conroy, L., Moran, M., **Pola ,P.** and McCormick, F. 1992 Molecular coloning and nucleic acid binding properties of the GAP-associated tyrosine phosphoprotein p62. **Cell** 69, 551-558.

24. Polakis, P., Rubinfeld, B. and McCormick, F. 1992 Phosphorylation of rap1GAP in vivo and by cAMP-dependent Kinase and the Cell Cycle $p34^{cdc2}$ Kinase in vitro. **J. Biol. Chem.** 267, 10780-10785.

25. McCabe, P.C., Haubrauck, H., **Polakis, P.**, McCormick, F., and Innis, M. A. 1992 Functional Interactions Between $p21^{rap1A}$ and Components of the Budding pathway of *Saccharomyces cerevisiae*. **Mol. Cell. Biol.** 12, 4084-4092.

26. Rubinfeld, B., Crosier, W.J., Albert, I., Conroy,L., Clark, R., McCormick, F. and **Polakis, P.** 1992 Localization of the rap1GAP Catalytic Domain and Sites of Phosphorylation by Mutational Analysis. **Mol. Cell . Biol.** 12, 4634-4642.

27. Ando, S., Kaibuchi, K., Sasaki, K., Hiraoka, T., Nishiyama, T., Mizuno, T., Asada, M., Nunoi, H., Matsuda, I., Matsuura, Y., **Polakis, P.**, McCormick, F. and Takai, Y. 1992 Post-translational processing of rac p21s is important both for their interaction with the GDP/GTP exchange proteins and for their activation of NADPH oxidase. **J. Biol. Chem.** 267, 25709-25713.

28. Janoueix-Lerosey, I., **Polakis, P.**, Tavitian, A. and deGunzberg, J. 1992 Regulation of the GTPase activity of the ras-related rap2 protein. **Biochem. Biophys. Res. Commun.** 189, 455-464.

29. Polakis, P. 1993 GAPs Specific for the rap1/Krev-1 Protein. in GTP-binding Proteins: the *ras*-superfamily. (J.C. LaCale and F. McCormick, eds.) 445-452.

30. Polakis, P. and McCormick, F. 1993 Structural requirements for the interaction of $p21^{ras}$ with GAP, exchange factors, and its bological effector target. **J. Biol Chem.** 268, 9157-9160.

31. Rubinfeld, B., Souza, B. Albert, I., Muller, O., Chamberlain, S., Masiarz, F., Munemitsu, S. and **Polakis, P.** 1993 Association of the APC gene product with beta- catenin. **Science** 262, 1731-1734.

32. Weiss, J., Rubinfeld, B., **Polakis, P.**, McCormick, F. Cavenee, W. A. and Arden, K. 1993 The gene for human rap1-GTPase activating protein (rap1GAP) maps to chromosome 1p35-1p36.1. **Cytogenet. Cell Genet.** 66, 18-21.

33. Sato, K. Y., **Polakis, P.**, Haubruck, H., Fasching, C. L., McCormick, F. and Stanbridge, E. J. 1994 Analysis of the tumor suppressor acitvity of the K-rev gene in human tumor cell lines. **Cancer Res.** 54, 552-559.

34. Janoueix-Lerosey, I., Fontenay, M., Tobelem, G., Tavitian, A., **Polakis, P.** and DeGunzburg, J. 1994 Phosphorylation of rap1GAP during the cell cycle. **Biochem. Biophys. Res. Commun.** 202, 967-975

35. Munemitsu, S., Souza, B., Mueller, O., Albert, I., Rubinfeld, B., and **Polakis, P.** 1994 The APC gene product associates with microtubules in vivo and affects their assembly in vitro. **Cancer Res.** 54, 3676-3681.

36. Rubinfeld, B. and **Polakis, P.** 1995 Purification of baculovirus produced rap1GAP.. **Methods Enz.** 255,31

37. **Polakis, P.** 1995 Mutations in the APC gene and their implications for protein structure and function. **Current Opinions in Genetics and Development** 5, 66-71

38. Rubinfeld, B., Souza, B., Albert, I., Munemitsu, S. and **Polakis P.** 1995 The APC protein and E-cadherin form similar but independent complexes with α-catenin, β-catenin and Plakoglobin. **J. Biol. Chem.** 270, 5549-5555

39. Munemitsu, S., Albert, I., Souza, B., Rubinfeld, B., and **Polakis, P.** 1995 Regulation of intracellular β-catenin levels by the APC tumor suppressor gene. **Proc. Natl. Acad. Sci.** 92, 3046-3050.

40. Lock, P., Fumagalli, S., **Polakis, P.** McCormick, F. and Courtneidge, S. A. 1996 The human p62 cDNA encodes Sam68 and not the rasGAP-associated p62 protein. **Cell** 84, 23-24.

41. Papkoff, J., Rubinfeld, B., Schryver, B. and **Polakis, P.** 1996 Wnt-1 regulates free pools of catenins and stabilizes APC-catenin complexes. **Mol. Cell. Biol.** 16, 2128-2134.

42. Rubinfeld, B., Albert, I., Porfiri, E., Fiol, C., Munemitsu, S. and **Polakis, P.** 1996 Binding of GSK3β to the APC-β-catenin complex and regulation of complex assembly. **Science** 272, 1023-1026.

43. Munemitsu, S., Albert, I., Rubinfeld, B. and **Polakis, P.** 1996 Deletion of amino-terminal structure stabilizes β-catenin in vivo and promotes the hyperphosphorylation of the APC tumor suppressor protein. **Mol. Cell. Biol.**16, 4088-4094.

44. Hart, M. J., Callow, M. G., Sousa, B. and **Polakis P.** 1996 IQGAP1, a calmodulin binding protein witha rasGAP related domain, is a potential effector for cdc42Hs. **EMBO J.** 15, 2997-3005.

45. Nathke, I. S., Adams, C. L., **Polakis, P.**, Sellin, J. and Nelson, W. J. 1996 The adenomatous polyposis coli (APC) tumor suppressor protein is localized to plasma membrane sites involved in active epithelial cell migration. **J. Cell. Biol.** 134, 165-180.

46. Hart, M. J., Sharma, S., elMasry, N., Qui, R-G., McCabe, P., **Polakis, P.** and Bollag, G. 1996 Identification of a novel guanine nucleotide exchange factor for the rho GTPase. **J. Biol. Chem.** 271, 25452.

47. Thomas JE, Smith M, Rubinfeld B, Gutowski M, Beckmann RP, and **Polakis P.** 1996 Subcellular localization and analysis of apparent 180-kDa and 220-kDa proteins of the breast cancer susceptibility gene, BRCA1. **J. Biol. Chem.** 1996 271, 28630-28635

48. Hayashi, S., Rubinfeld, B., Souza, B., **Polakis, P.**, Wieschaus, E., and Levine, A. 1997 A Drosophila homolog of the tumor suppressor adenomatous polyposis coli

down-regulates β -catenin its zygotic expression is not esse l for the regulation of armadillo. **Proc. Natl. Acad. Sci.** 94, 242-247.

49. Vleminckx, K., Rubinfeld, B., **Polakis, P.** and Gumbiner, B. 1997 The APC tumor suppressor protein induces a new axis in Xenopus embryos. **J. Cell. Biol.** 136, 411-420.

50. Rubinfeld, B., Robbins, P., El-Gamil, M., Albert, I., Porfiri, P. and **Polakis, P.** 1997 Stabilization of β-catenin by genetic defects in melanoma cell lines. **Science** 275, 1790-1792.

51. Polakis, P. The adenomatous polyposis coli (APC) tumor suppressor. 1997 **Biochem. Biophys. Acta**, 1332, F127-F147.

52. Rubinfeld, B., Albert, I., Porfiri, E., Munemitsu, S., and **Polakis, P** 1997 Loss of β-catenin regulation by the APC tumor suppressor protein correlates with loss of structure due to common somatic mutations of the gene. **Cancer Res.** 57, 4624-4630.

53. Porfiri, E., Rubinfeld, B., Albert, I., Hovanes. K., Waterman, M., and **Polakis, P.** 1997 Induction of a β-catenin-LEF-1 complex by wnt-1 and transforming mutants of β-catenin. **Oncogene** 15, 2833-2839.

54. Thomas JE, Smith M, Tonkinson JL, Rubinfeld B, and **Polakis P.**, 1997 Induction of phosphorylation on BRCA1 during the cell cycle and after DNA damage. **Cell Growth Differ.** 8, 801-809.

55. Hart, M., de los Santos, R., Albert, I., Rubinfeld, B., and **Polakis P.**, 1998 Down regulation of β-catenin by human Axin and its association with the adenomatous polyposis coli (APC) tumor suppressor, β-catenin and glycogen synthase kinase 3β. **Current Biology 8,** 573-581.

56. Polakis, P. 1998 The oncogenic activation of β-catenin. **Current Opinions in Genetics and Development** 9, 15-21

57. Matt Hart, Jean-Paul Concordet, Irina Lassot, Iris Albert, Rico del los Santos, Herve Durand, Christine Perret, Bonnee Rubinfled, Florence Margottin, Richard Benarous and **Paul Polakis.** 1999 The F-box protein β–TrCP associates with phosphorylated β–catenin and regulates its activity in the cell. **Current Biology** 9, 207-10.

58. Howard C. Crawford, Barbara M. Fingleton, Bonnee Rubinfeld, **Paul Polakis** and Lynn M. Matrisian 1999 The metalloproteinase matrilysin is a target of β–catenin transactivation in intestinal tumours. **Oncogene** 18, 2883-91.

59. Meng J, Glick JL, **Polakis P**, Casey PJ. 1999 Functional interaction between Galpha(z) and Rap1GAP suggests a novel form of cellular cross-talk. **J Biol Chem.** 17, 36663-9

60. Vijayasurian Easwaran rginia Song, **Paul Polakis** and St Byers 1999 The ubiquitin-proteosome pathway and serine kinase activity modulate APC mediated regulation of β-catenin-LEF signaling. **J. Biol. Chem.** 274(23):16641-5.

61 Polakis P, Hart M and Rubinfeld B. 1999 Defects in the regulation of beta-catenin
in colorectal cancer. **Adv Exp Med Biol.** 470, 23-32

62 Shen Z, Batzer A, Koehler JA, **Polakis P**, Schlessinger J, Lydon NB, Moran MF. 1999 Evidence for SH3 domain directed binding and phosphorylation of Sam68 by Src. **Oncogene.** 18, 4647-53

64. Thomas GM, Frame S, Goedert M, Nathke I, **Polakis P**, Cohen P. 1999 A GSK3- binding peptide from FRAT1 selectively inhibits the GSK3-catalysed phosphorylation of axin and beta-catenin. **FEBS Lett.** 458, 247-51.

65. Peifer M, **Polakis P.** 2000 Wnt signaling in oncogenesis and embryogenesis--a look outside the nucleus. **Science** 287,1606-9.

66. **Polakis P.** 2000 Wnt signaling and cancer. **Genes Dev**;14, 1837-1851.

67. Spink KE, **Polakis P**, Weis WI 2000 Structural basis of the Axin-adenomatous polyposis coli interaction. **EMBO J** 19, 2270-2279.

68. Szeto , W., Jiang, W., Tice, D.A., Rubinfeld, B., Hollingshead, P.G., Fong, S.E., Dugger, D.L., Pham, T., Yansura, D.E., Wong, T.A., Grimaldi, J.C., Corpuz, R.T., Singh J.S., Frantz, G.D., Devaux, B., Crowley, C.W., Schwall, R.H., Eberhard, D.A.,
Rastelli, L., **Polakis, P.** and Pennica, D. 2001 Overexpression of the Retinoic Acid-
Responsive Gene Stra6 in Human Cancers and its Synergistic Induction by Wnt-1 and
Retinoic Acid. **Cancer Res** 61, 4197-4204.

69. Rubinfeld B, Tice DA, **Polakis P.** 2001 Axin dependent phosphorylation of the adenomatous polyposis coli protein mediated by casein kinase 1 epsilon. **J Biol Chem**
276, 39037-39045.

70. **Polakis P.** 2001 More than one way to skin a catenin. **Cell** 2001 105, 563-566.

71. Tice DA, Soloviev I, **Polakis P.** 2002 Activation of the Wnt Pathway Interferes withSerum Response Element-driven Transcription of Immediate Early Genes. **J Biol.**
Chem. 277, 6118-6123.

72. Tice DA, Szeto W, Soloviev I, Rubinfeld B, Fong SE, Dugger DL, Winer J,

Williams PM, Wieand D, S[illegible] V, Schwall RH, Pennnica D, **Pol[illegible]s P.** 2002 Synergistic activation of tumor antigens by wnt-1 signaling and retinoic acid revealed by gene expression profiling. **J Biol Chem.** 277,14329-14335.

73. **Polakis, P.** 2002 Casein kinase I: A wnt'er of disconnect. **Curr. Biol.** 12, R499.

74. Mao,W. , Luis, E., Ross, S., Silva, J., Tan, C., Crowley, C., Chui, C., Franz, G., Senter, P., Koeppen, H., **Polakis, P.** 2004 EphB2 as a therapeutic antibody drug target for the treatment of colorectal cancer. **Cancer Res.** 64, 781-788.

75. Shibamoto, S., Winer, J., Williams, M., Polakis, P. 2003 A Blockade in Wnt signaling is activated following the differentiation of F9 teratocarcinoma cells. **Exp. Cell Res.** 29211-20.

76. Zhang Y, Eberhard DA, Frantz GD, Dowd P, Wu TD, Zhou Y, Watanabe C, Luoh SM, **Polakis P,** Hillan KJ, Wood WI, Zhang Z. 2004 GEPIS--quantitative gene expression profiling in normal and cancer tissues. **Bioinformatics,** April 8

SECOND DECLARATION OF PAUL POLAKIS, Ph.D.

I, Paul Polakis, Ph.D., declare and say as follows:

1. I am currently employed by Genentech, Inc. where my job title is Staff Scientist.

2. Since joining Genentech in 1999, one of my primary responsibilities has been leading Genentech's Tumor Antigen Project, which is a large research project with a primary focus on identifying tumor cell markers that find use as targets for both the diagnosis and treatment of cancer in humans.

3. As I stated in my previous Declaration dated May 7, 2004 (attached as Exhibit A), my laboratory has been employing a variety of techniques, including microarray analysis, to identify genes which are differentially expressed in human tumor tissue relative to normal human tissue. The primary purpose of this research is to identify proteins that are abundantly expressed on certain human tumor tissue(s) and that are either (i) not expressed, or (ii) expressed at detectably lower levels, on normal tissue(s).

4. In the course of our research using microarray analysis, we have identified approximately 200 gene transcripts that are present in human tumor tissue at significantly higher levels than in normal human tissue. To date, we have successfully generated antibodies that bind to 31 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human tumor tissue and normal tissue. We have then quantitatively compared the levels of mRNA and protein in both the tumor and normal tissues analyzed. The results of these analyses are attached herewith as Exhibit B. In Exhibit B, "+" means that the mRNA or protein was detectably overexpressed in the tumor tissue relative to normal tissue and "-" means that no detectable overexpression was observed in the tumor tissue relative to normal tissue.

5. As shown in Exhibit B, of the 31 genes identified as being detectably overexpressed in human tumor tissue as compared to normal human tissue at the mRNA level, 28 of them (i.e., greater than 90%) are also detectably overexpressed in human tumor tissue as compared to normal human tissue at the protein level. As such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA.

6. Based upon my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4-5 above and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor tissue relative to a normal tissue more often than not correlates to a similar increase in abundance of the encoded protein in the tumor tissue relative to the normal tissue. In fact, it remains a generally accepted working assumption in molecular biology that increased mRNA levels are more often than not predictive of elevated levels of the encoded protein. In fact, an entire industry focusing on the research and development of therapeutic antibodies to treat a variety of human diseases, such as cancer, operates on this working assumption.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 3-29-06

By: Paul Polakis

Paul Polakis, Ph.D.

EXHIBIT B

	tumor mRNA	tumor IHC
UNQ2525	+	+
UNQ2378	+	+
UNQ972	+	-
UNQ97671	+	+
UNQ2964	+	+
UNQ323	+	+
UNQ1655	+	+
UNQ2333	+	+
UNQ9638	+	+
UNQ8209	+	+
UNQ6507	+	+
UNQ8196	+	+
UNQ9109	+	+
UNQ100	+	+
UNQ178	+	+
UNQ1477	+	+
UNQ1839	+	+
UNQ2079	+	+
UNQ8782	+	+
UNQ9646	+	-
UNQ111	+	+
UNQ3079	+	+
UNQ8175	+	+
UNQ9509	+	+
UNQ10978	+	-
UNQ2103	+	+
UNQ1563	+	+
UNQ16188	+	+
UNQ13589	+	+
UNQ1078	+	+
UNQ879	+	+

DECLARATION OF RANDY SCOTT, Ph.D. UNDER 37 C.F.R. § 1.132

I, Randy Scott, Ph.D. declare and say as follows:

1. I hold a Bachelor or Science degree in Chemistry from Emporia State University and a Ph.D. in Biochemistry from the University of Kansas.

2. I am Chairman and Chief Executive Officer of Genomic Health, Inc., a life science company founded in August of 2000 located in Redwood City, California, conducting sophisticated genomic research to develop clinically validated molecular diagnostics, which provide individualized information on the likelihood of disease recurrence and response to certain types of therapy.

3. In 1991, I co-founded Incyte Pharmaceuticals, Inc., the world's first genomic information business. I served the company in multiple capacities, including Chairman of the Board from August 2000 to December 2001, President from January 1997 to August 2000, and Chief Scientific Officer from March 1995 to August 2000. Under my leadership, Incyte has created the LifeSeq Gold® gene sequence and expression database, an industry standard and the most comprehensive collection of biological information in the world. I have also led Incyte to expand its focus beyond gene sequence databases to include the research and application of gene expression, SNPs (single nucleotide polymorphisms), and proteomics.

4. I am an inventor on several issued patents, and authored over 40 scientific publications in the fields of protein biology, gene discovery, and cancer.

5. My Curriculum Vitae is attached to and serves part of this Declaration.

6. All statements made in this Declaration are based on my more than 15 years of personal experience with the DNA microarray technique and its various uses in the diagnostic and therapeutic fields, and my familiarity with the relevant art.

7. The DNA microarray technology is based on hybridizing arrayed nucleic acid probes of known identity with target nucleic acid to determine the identity and/or expression levels (abundance) of target genes. DNA microarrays work by exploiting the ability of a given

mRNA molecule to hybridize to the DNA template from which it originated. By using an array containing many DNA samples, scientists can determine, in a single experiment, the expression levels of hundreds or thousands of genes within a sample by measuring the amount of mRNA bound to each site on the array. The amount of mRNA bound to the spots on the microarray is precisely measured, generating a profile of gene expression in the sample.

8. DNA microarray analysis has been extensively used in drug development and in diagnosis of various diseases. For instance, if a certain gene is over-expressed in a particular form of cancer relative to normal tissue, researchers use microarray chips to determine whether a drug candidate will reduce over-expression, and thereby cause cancer remission. In addition, if a gene has been identified to be over-expressed in a certain disease, such as a certain type of cancer, it can be used to diagnose that disease. Due to its importance in drug discovery and in the field of diagnostics, microarray technology has not only become a laboratory mainstay but also created a world-wide market of over $600 million in the year of 2005. A long line of companies, including Incyte, Affymetix, Agilent, Applied Biosystems, and Amersham Biosciences, made microarray technology a core of their business.

9. Correlation between mRNA and protein levels can be assessed by a variety of methods suitable for measuring protein expression levels, including, for example, SDS-polyacrylamide gel electrophoresis (SDS-PAGE), two-dimensional fluorescence-difference gel electrophoresis (DIGE), mass spectrometric approaches, microsequencing, and a combination of these and similar known techniques, however, direct measurement of protein expression levels remains non-trivial.

10. One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, without the need to directly measure individual protein expression levels.

11. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the Patent.

Date: August 11, 2006

Randy Scott, Ph.D.

SV 2202107 v1
8/11/06 11:00 AM (39766.7000)

Randy W. Scott, Ph.D.
Genomic Health
301 Penobscot
Redwood City, CA 94022

EDUCATION:

1979 B.S., Chemistry, Emporia State University, Emporia Kansas
1983 Ph.D., Biochemistry, University of Kansas, Lawrence Kansas

WORK EXPERIENCE:

2000-present **GENOMIC HEALTH, INC., Cofounder**

- *Chairman & CEO, (2000-present)*
  Founded a new genomics company and raised over $100 million to bring personalized medicine to clinical practice. Selected by Red Herring Magazine as one of the Top 100 private technology companies in North America in 2005

1991-2000 **INCYTE, Cofounder**

- *Chairman of the Board (2000-2001)*
  Helped lead the transition to a new management team and transition to drug development
- *President and Chief Scientific Officer (1997-2000)*
  Responsible for Research & Development, Operations, Marketing & Sales. Built the world's first genomic information business with peak sales of over $200 million per year including 19 out of the worlds top 20 pharmaceutical companies as subscribers
- *Vice President and Chief Scientific Officer (1991-1997)*
  Built recombinant DNA therapeutic product portfolio and led the launch of the genomics business

1985-91 **INVITRON CORPORATION**

- *Sr. Director of Research (1998-1991)*
  Responsible for Research & Development.
- *Director of Protein Biochemistry (1985-1988)*
  Responsible for building the protein purification group for a cGMP manufacturing facility producing recombinant proteins, including monoclonal antibodies, tPA and Factor VIII.

1983-85 **UNIGENE LABORATORIES, Fairfield, New Jersey**

- *Sr. Scientist, Dept. of Protein Biochemistry*
  Led effort to work on IgA proteases linked to meningococcal infections

OTHER EXPERIENCE:

2005- Present **AMERICAN CLINICAL LABORATORY ASSOCIATION**

- *Member, Board of Directors*

1997-2000 **DIADEXUS, INC., Cofounder**

- *Member, Board of Directors, (1997-2000)*
  Worked with George Poste (CSO, SmithKline, Beecham) to establish a diagnostics joint venture between Incyte and SmithKline

Awards:

2001 Genome Technology Magazine 2001 All-Star
1999 Forbes Magazine list of Biotech's Top 25 Influential Insiders
1997 Ernst & Young/NASDAQ Silicon Valley Entrepreneur of the Year for Life Sciences
1987 Small Business Innovation Research Grant Award (Principal Investigator): "Azurophil-Derived Bactericidal Factor" Grant # SSS-5 (K) 1R43AI24409-011987
1983 Phillip Newmark Research Award, University of Kansas, 1983
1982 Borgendale Graduate Seminar Award, University of Kansas.

Publications:

Low, D.A., Cunningham, D.D., **Scott, R.W.**, and Baker, J.B., "Interactions of Serine Proteases with Human Fibroblasts: Regulation by Protease Nexin. A Cellular Component with Similarities to Antithrombin III." in Receptor-Mediated Binding

Low, D.A., **Scott, R.W.**, Baker J.B., and Cunningham, D.D., Cells Regulate their Mitogenic Response to Thrombin through Release of Protease Nexin. Nature 298, 476-478 (1982).

Scott, R.W. ,"Purification, Characterization, and Functional Studies of Protease Nexin." Ph.D. Thesis, University of Kansas (1983).

Scott, R.W., Eaton, D.L., Duran, N. and Baker, J.B. Regulation of Extracellular Plasminogen Activator by Human Fibroblasts. The Role of Protease Nexin. J. Biol. Chem. 258, 4397-4403 (1983).

Scott, R.W., and Baker, J.B., Purification of Human Protease Nexin. J.Biol. Chem. 258, 10439-10444 (1983).

Eaton, D.L., **Scott, R.W.**, and Baker, J.B., Purification of Human Fibroblast Urokinase Proenzyme and Analysis of its Regulation by Proteases and Protease Nexin. J. Biol. Chem. 259, 6241-6247 (1984).

Scott, R.W., Bergman, B., Bajpai, A., Hersh, R., Rodriquez, H., Jones, B.N., Barreda, C., Watts, S., and Baker, J.B. Protease Nexin: Properties and a Modified Purification Procedure. J.Biol. Chem. 7029-7034 (1985).

Bergman, B.L., **Scott, R.W.**, Bajpai, A., Watts, S., and Baker, J.B., Inhibition of Tumor-Cell Extracellular Matrix Destruction by a Fibroblast Proteinase Inhibitor, Protease Nexin I. Proc. Nat. Acad. Sci. 83, 996-1000 (1986).

Cance, W.G., Wells, S.A., Dilley, W.G., Welch, M.J., Otsuka, F.L., **Scott, R.W.**, and Davie, J.M., Unique Parathyroid Membrane Antigen(s): Radiolocalization with Specific Monoclomal Antibodies. Surgical Form 37, 410-412 (1986).

Scott, R.W., Duffy, S.A., Moellering, B.J., and Prior, C., Purification of Monoclonal Antibodies from Large-Scale Mammalian Cell Culture Perfusion Systems. Biotechnology Progress 3, 49-56 (1987).

Baker, J.B., McGrogan, M., Simonsen, C.C., **Scott, R.W.**, Gronke, R.S. and Honeyman, A., "Protease Nexin I. Structure and Potential Functions." In The Pharmacology and Toxicology of Proteins, Winkelhake, J.L., Holcenberg, J.S., eds., Alan R. Liss, Inc., New York, (1987).

Scott R.W., "Large-scale Production of Biopharmaceuticals from Mammalian Cells" in Clinical Applications of Genetic Engineering (Larry C. Lasky and JoAnn Edwards-Moulds eds.) American Association of Blood Banks, Arlington, Virginia (1987).

McGrogan, M., Kennedy, J., Li, M.P., Hsu, C., **Scott, R.W.**, Simonsen, C.C., and Baker, J.B., Molecular Cloning and Expression of Two Forms of Human Protease Nexin I, Bio/Technology 6: 172 (1988).

Otsuka FL, Cance WG, Dilley WG, **Scott RW**, Davie JM, Welch MJ, Wells SA Jr., A Potential New Radiopharmaceutical for Parathyroid Imaging: Radiolabeled Parathyroid-specific Monoclonal Antibody –I. Evaluation of 125-I-labeled Antibody in a Nude Mouse Model System. Int. J. Rad. Appl. Instrum. B. 15:305-11, 1988

Otsuka FL, Cance WG, Dilley WG, **Scott RW**, Davie JM, Wells SA Jr., Welch MJ A Potential New Radiopharmaceutical for Parathyroid Imaging: Radiolabeled Parathyroid-specific Monoclonal Antibody –II. Comparison of 125-I and 111-In-labeled Antibodies. Int. J. Rad. Appl. Instrum. B. 15:305-11, 1988

Prior, C.P., Doyle, K.R., Duffy, S.A., Hope, J.A., Moellering, B.J., Prior, G.M., **Scott, R.W.** and Tolbert, W.R. The Recovery of Highly Purified Biopharmaceuticals from Perfusion Cell Culture Bioreactors. J. Parenteral Science and Technology 43: 15-23 (1989).

McGrogan, M., Simonsen, C., **Scott, R.**, Griffith, J., Ellis, N., Kennedy, J., Campanelli, D., Nathan, C., and Gabay, J., Isolation of a Complementary DNA Clone Encoding a Precursor to Human Eosinophil Major Basic Protein. J. Exp. Med. 168: 2295-2308 (1988).

Wilde, C.G., Griffith, J.E., Marra, M.N., Snable, J.L. and **Scott R.W.**, Purification and Characterization of Human Neutrophil Peptide 4, a Novel Member of the Defensin Family, J. Biol. Chem. 264: 11200-11203 (1989).

Gabay, J.E., **Scott, R.W.**, Campanelli, D., Griffith, J., Wilde, C., Marra, M.N., Seeger, M., and Nathan, C.F., Antibiotic Proteins of Human Polymorphonuclear Leukocytes, Proc. Natl. Acad. Sci. 86: 5610-5614 (1989).

Marra , M.N., Wilde, C.G., Griffith, J.E., Snable, J.L., and **Scott R.W.**, Bactericidal/Permeability-Increasing Protein has Endotoxin Neutralizing Activity, J. Immunol. 144, 662-666 (1990)

Moellering, B.J., Tedesco, J.L., **Scott, R.W.**, Towensend, R.R., Hardy, M.R., and Prior C.P. Molecular Differences Observed in a Monoclonal Antibody Expressed in Ascites Fluid, Serum-containing and Serum-free Cell Culture Conditions. Biopharm. pp. 30-38 February (1990).

McGrogan, M., Kennedy, J., Golini, F., Ashton, N., Dunn, F., Bell, K., Tate, E., **Scott, R.W.**, and Simonsen, C.C., "Structure of the Human Protease Nexin Gene and Expression of Recombinant forms of PN-1." in Serine Proteases and Serpins in the Nervous System (B.W. Festoff ed.) pp.147-161 Plenum Press New York (1990).

Pereira, H.A., Spitznagel, J.K., Winton, E.F., Shafer, W.M., Martin, L.E., Guzman, G.S. Pohl, J., **Scott, R.W.**, and Kinkade, J.M. Jr. The Ontogeny of a 57KD Cationic Antimicrobial Protein of Human Polymorphonuclear Leukocytes: Localization to a Novel Granule Population. Blood 76:825-834, 1990.

Evans DL, McGrogan M, **Scott RW**, Carrell RW, Protease Specificity and Heparin Binding and Activation of Recombinant Protease Nexin I, J. Biol. Chem. 266:22307-12, 1991

Marra, M,N, C.G. Wilde, M.S. Collins, J.L. Snable, M.B. Thornton, and **R.W. Scott,** The Role of Bactericidal/Permeability-Increasing Protein as a Natural Inhibitor of Bacterial Endotoxin. J. of Immunol. 148:532-537, 1992.

Scott R. W., Wilde C.G., Lane J.C., Snable, J.L., and Marra M.N., "Antimicrobial and Antiendotoxin Activities of Bactericidal/Permeability-Increasing Protein In Vitro and In Vivo" in Bacterial Endotoxin: Recognition and Effector Mechanisms (J. Levin, C.R. Alving, R.S. Munford, and P.L. Stutz eds.) pp. 373-377 Elsevier Science Publishers B.V. (1993)

Stevens, P., **Scott R.W.**, Shatzen E.M., Recombinant Human Protease Nexin-1 Prevents Articular Cartilage Degradation in the Rabbit Agents and Actions Suppl 39:173-7 in press 1993

Marra M.N., Thornton, M.B., Snable, J.L., Leong S., Lane J., Wilde C.G., and **Scott R. W.**, Regulation of the Response to Bacterial Lipopolysaccharide by Endogenous and Exogenous Lipopolysaccharide Binding Proteins" Blood Purif. 11:134-140, 1993

Scott RW, Sequencing the Human Genome (letter), Science 30 260:606-7 1993

Marra M.N., Thornton M.B., Snable J.L., Wilde C.G., **Scott R.W.**, Endotoxin-binding and -neutralizing Properties of Recombinant Bactericidal/Permeability-Increasing Protein and Monoclonal Antibodies HA-1A and E5 Critical Care Medicine 22:559-65, 1994

Fisher CJ Jr., Marra MN, Palardy JE, Marchbanks CR, **Scott RW**, Opal SM Human Neutrophil Bactericidal/Permeability-Increasing Protein Reduces Mortality Rate from Endotoxin Challenge: a Placebo-Controlled Study. Crit Care Med 22:553-8, 1994

Rogy MA, Oldenburg HS, Calvano SE, Montegut WJ, Stackpole SA, Van Zee KJ, Marra MN, **Scott RW**, Seilhammer JJ, Moldawer LL. The Role of Bactericidal/Permeability-Increasing Protein in the Treatment of Primate Bacteremia and Septic Shock. J Clin. Immunol. 14: 120-33, 1994

Calvano SE, Thompson WA, Marra MN, Coyle SM, de Riesthal HF, Trousdale RK, Barie PS, **Scott RW**, Moldawer LL, Lowry SF, Changes in Polymorphonuclear Leukocyte Surface and Plasma Bactericidal/Permeability-Increasing Protein and Plasma Lipopolysaccharide Binding Protein During Endotoxemia or Sepsis. Arch Surg. 129:220-6, 1994

Wilde, G.G., Seilhamer, J.J., McGrogan, M., Ashton, N., Snable, J.L., Lane JC, Leong, SR, Thornton, MB, Miller, KL, **Scott RW**, and Marra, MN "Bactericidal/Permeability-Increasing Protein and Lipopolysaccharide (LPS)-Binding Protein: LPS Binding Properties and Effects on LPS-Mediated Cell Activation" J. Biol. Chem. 269:17411-17416, 1994

Wilde CG, Hawkins PR, Coleman RT, Levine WB, Delegeane AM, Okamoto PM, Ito LY, **Scott RW**, Seilhamer JJ, DNA Cell Biol. 13:711-8, 1994

Opal SM, Palardy JE, Marra MN, Fisher CJ Jr., McKelligon BM, **Scott RW** Lancet 344:429-31 1994

Yang, JH, Marsters, S., Ashkenazi A., Bunting S, Marra MN, **Scott RW**, Baker JB Protection against endotoxic shock by Bactericidal/permeability-increasing Protein in Rats, J. Clin. Invest. 95:1947-52, 1995

Scott RW, Gene Patents and Other Genomic Inventions. Published Hearing before the Subcommittee on Courts and Intellectual Property of the Committee on the Judiciary House of Representatives, One Hundred Sixth Congress, Second Session, July 13, 2000 Serial No. 121. pp. 44-55 . U.S. Government Printing Office Washington, 2000

Issued Patents:

U.S. Patent # 4,898,826 Issued Feb. 6, 1990
A Method for Solubilization of Tissue-Type Plasminogen Activator.

U.S. Patent # 5,006,252 Issued April 9, 1991
Recombinant Purified Protease Nexin.

U.S. Patent #5,032,574 Issued July 16, 1991
Novel Antimicrobial Peptide, Compositions Containing Same and Uses Thereof.

U.S. Patent #5,087,368 Issued Feb. 11, 1992
Purified Protease Nexin

U.S. Patent #5,089,274 Issued Feb. 18, 1992
Use of Bactericidal/Permeability Increasing Protein or Biologically Active Analogs Thereof to Treat Endotoxin-Related Disorders

U.S. Patent #5,112,608 Issued May 12, 1992
Use of Protease Nexin-1 to Mediate Wound Healing

U.S. Patent #5,171,739 Issued December 15, 1992
Treatment of Endotoxin-Associated Shock and Prevention Thereof Using a BPI Protein

U.S. Patent #5,187,089 Issued Feb. 16, 1993
Protease Nexin-1 Variants Which Inhibit Elastase

U.S. Patent #5,196,196 Issued March 23, 1993
Use of Protease Nexin-1 in Wound Dressings

U.S. Patent #5,206,017 Issued Apr. 27, 1993
Use of Protease Nexin-1 as an Anti-inflammatory

U.S. Patent #5,210,027 Issued May 11, 1993
DNA Encoding Novel Antimicrobial Polypeptide and Methods for Obtaining Such Polypeptide

U.S. Patent #5,278,049 Issued January 11, 1994
Recombinant Molecule encoding Human Protease Nexin

U.S. Patent #5,234,912 Issued August 10, 1993
Pharmaceutical Compositions Comprising Recombinant BPI Proteins and a Lipid Carrier and Uses Thereof

U.S. Patent #5,278,049 Issued January 11, 1994
Recombinant Molecule encoding Human Protease Nexin

U.S. Patent #5,308,834 Issued May 3, 1994
Treatment of Endotoxin-Associated Shock and Prevention Thereof Using BPI Protein

U.S. Patent #5,326,562 Issued July 5, 1994
Pharmaceutical Dosage Unit for Treating Inflammation Comprising Protease Nexin-I

U.S. Patent #5,234,912 Issued August 10, 1993
Pharmaceutical Compositions Comprising Recombinant BPI Proteins and a Lipid Carrier and Uses

U.S. Patent #5,278,049 Issued January 11, 1994
Recombinant Molecule Encoding Human Protease Nexin

U.S. Patent #5,326,562 Issued July 5, 1994
Pharmaceutical Dosage Unit for Treating Inflammation Comprising Protease Nexin-1

Recombinant, Non-Glycosylated BPI Protein and Uses Thereof

U.S. Patent #5,457,090 Issued October 10, 1995
Protease Nexin-I Variants

U.S. Patent #5,470,825 Issued November 28, 1995
Basophil Granule Proteins

U.S. Patent #5,476,839 Issued December 19, 1995
Basophil Granule Proteins

U.S. Patent #5,495,001 Issued February 27, 1996
Recombinant Purified Protease Nexin

U.S. Patent #5,747,283 Issued May 5, 1998
Basophil Granule Proteins

U.S. Patent #5,770,694 Issued June 23, 1998
Genetically Engineered BPI Variant Proteins

U.S. Patent #5,840,484 Issued November 24, 1998
Comparative Gene Transcript Analysis

U.S. Patent #6,114,114 Issued September 5, 2000
Comparative Gene Transcript Analysis

U.S. Patent #6,093,801 Issued July 25, 2000
Recombinant Analogs of Bactericidal/Permeability Increasing Protein

U.S. Patent #6,160,104 Issued December 12, 2000
Markers for Peroxisomal Proliferators

U.S. Patent #6,160,105 Issued December 12, 2000
Monitoring Toxicological Responses

U.S. Patent #6,265,187 Issued July 24, 2001
Recombinant Endotoxin Neutralizing Proteins

U.S. Patent #6,403,778 Issued June 11, 2002
Toxicological Response Markers

U.S. Patent #6,372,431 Issued April 16, 2002
Mammalian Toxicological Response Markers

U.S. Patent #6,553,317 Issued April 22, 2003
Relational database and system for storing information relating to biomolecular sequences and reagents

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Ashkenazi et al.
App. No.	:	09/903,925
Filed	:	July 11, 2001
For	:	SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME
Examiner	:	Hamud, Fozia M

Group Art Unit 1647

CERTIFICATE OF EXPRESS MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to Commissioner of Patents, Washington D.C. 20231 on:

_____
(Date)

_____

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF AVI ASHKENAZI, Ph.D UNDER 37 C.F.R. § 1.132

I, Avi Ashkenazi, Ph.D. declare and say as follows: -

1. I am Director and Staff Scientist at the Molecular Oncology Department of Genentech, Inc., South San Francisco, CA 94080.

2. I joined Genentech in 1988 as a postdoctoral fellow. Since then, I have investigated a variety of cellular signal transduction mechanisms, including apoptosis, and have developed technologies to modulate such mechanisms as a means of therapeutic intervention in cancer and autoimmune disease. I am currently involved in the investigation of a series of secreted proteins over-expressed in tumors, with the aim to identify useful targets for the development of therapeutic antibodies for cancer treatment.

3. My scientific Curriculum Vitae, including my list of publications, is attached to and forms part of this Declaration (Exhibit A).

4. Gene amplification is a process in which chromosomes undergo changes to contain multiple copies of certain genes that normally exist as a single copy, and is an important factor in the pathophysiology of cancer. Amplification of certain genes (e.g., Myc or Her2/Neu)

gives cancer cells a growth or survival advantage relative to normal cells, and might also provide a mechanism of tumor cell resistance to chemotherapy or radiotherapy.

5. If gene amplification results in over-expression of the mRNA and the corresponding gene product, then it identifies that gene product as a promising target for cancer therapy, for example by the therapeutic antibody approach. Even in the absence of over-expression of the gene product, amplification of a cancer marker gene - as detected, for example, by the reverse transcriptase TaqMan® PCR or the fluorescence *in situ* hybridization (FISH) assays -is useful in the diagnosis or classification of cancer, or in predicting or monitoring the efficacy of cancer therapy. An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

6. I understand that according to the Patent Office, absent data demonstrating that the increased copy number of a gene in certain types of cancer leads to increased expression of its product, gene amplification data are insufficient to provide substantial utility or well established utility for the gene product (the encoded polypeptide), or an antibody specifically binding the encoded polypeptide. However, even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. •Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. •In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that wiliful false statements and the like so

made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

By: Avi Ashkenazi
Avi Ashkenazi, Ph.D.

Date: 9/15/03

CURRICULUM VITAE

Avi Ashkenazi

July 2003

Personal:

Date of birth:	29 November, 1956
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Education:

1983:	B.S. in Biochemistry, with honors, Hebrew University, Israel
1986:	Ph.D. in Biochemistry, Hebrew University, Israel

Employment:

1983-1986:	Teaching assistant, undergraduate level course in Biochemistry
1985-1986:	Teaching assistant, graduate level course on Signal Transduction
1986 - 1988:	Postdoctoral fellow, Hormone Research Dept., UCSF, and Developmental Biology Dept., Genentech, Inc., with J. Ramachandran
1988 - 1989:	Postdoctoral fellow, Molecular Biology Dept., Genentech, Inc., with D. Capon
1989 - 1993:	Scientist, Molecular Biology Dept., Genentech, Inc.
1994 -1996:	Senior Scientist, Molecular Oncology Dept., Genentech, Inc.
1996-1997:	Senior Scientist and Interim director, Molecular Oncology Dept., Genentech, Inc.
1997-1990:	Senior Scientist and preclinical project team leader, Genentech, Inc.
1999 -2002:	Staff Scientist in Molecular Oncology, Genentech, Inc.
2002-present:	Staff Scientist and Director in Molecular Oncology, Genentech, Inc.

Awards:

1988:	First prize, The Boehringer Ingelheim Award

Editorial:

Editorial Board Member: Current Biology

Associate Editor, Clinical Cancer Research.

Associate Editor, Cancer Biology and Therapy.

Refereed papers:

1. Gertler, A., Ashkenazi, A., and Madar, Z. Binding sites for human growth hormone and ovine and bovine prolactins in the mammary gland and liver of the lactating cow. *Mol. Cell. Endocrinol.* 34, 51-57 (1984).
2. Gertler, A., Shamay, A., Cohen, N., Ashkenazi, A., Friesen, H., Levanon, A., Gorecki, M., Aviv, H., Hadari, D., and Vogel, T. Inhibition of lactogenic activities of ovine prolactin and human growth hormone (hGH) by a novel form of a modified recombinant hGH. *Endocrinology* 118, 720-726 (1986).
3. Ashkenazi, A., Madar, Z., and Gertler, A. Partial purification and characterization of bovine mammary gland prolactin receptor. *Mol. Cell. Endocrinol.* 50, 79-87 (1987).
4. Ashkenazi, A., Pines, M., and Gertler, A. Down-regulation of lactogenic hormone receptors in Nb2 lymphoma cells by cholera toxin. *Biochemistry Internatl.* 14, 1065-1072 (1987).
5. Ashkenazi, A., Cohen, R., and Gertler, A. Characterization of lactogen receptors in lactogenic hormone-dependent and independent Nb2 lymphoma cell lines. *FEBS Lett.* 210, 51-55 (1987).
6. Ashkenazi, A., Vogel, T., Barash, I., Hadari, D., Levanon, A., Gorecki, M., and Gertler, A. Comparative study on in vitro and in vivo modulation of lactogenic and somatotropic receptors by native human growth hormone and its modified recombinant analog. *Endocrinology* 121, 414-419 (1987).
7. Peralta, E., Winslow, J., Peterson, G., Smith, D., Ashkenazi, A., Ramachandran, J., Schimerlik, M., and Capon, D. Primary structure and biochemical properties of an M2 muscarinic receptor. *Science* 236, 600-605 (1987).
8. Peralta, E. Ashkenazi, A., Winslow, J., Smith, D., Ramachandran, J., and Capon, D. J. Distinct primary structures, ligand-binding properties and tissue-specific expression of four human muscarinic acetylcholine receptors. *EMBO J.* 6, 3923-3929 (1987).
9. Ashkenazi, A., Winslow, J., Peralta, E., Peterson, G., Schimerlik, M., Capon, D., and Ramachandran, J. An M2 muscarinic receptor subtype coupled to both adenylyl cyclase and phosphoinositide turnover. *Science* 238, 672-675 (1987).

10. Pines, M., Ashkenazi, A., Cohen-Chapnik, N., Binder, L., and Gertler, A. Inhibition of the proliferation of Nb2 lymphoma cells by femtomolar concentrations of cholera toxin and partial reversal of the effect by 12-o-tetradecanoyl-phorbol-13-acetate. *J. Cell. Biochem.* **37**, 119-129 (1988).

11. Peralta, E. Ashkenazi, A., Winslow, J. Ramachandran, J., and Capon, D. Differential regulation of PI hydrolysis and adenylyl cyclase by muscarinic receptor subtypes. *Nature* **334**, 434-437 (1988).

12. Ashkenazi., A. Peralta, E., Winslow, J., Ramachandran, J., and Capon, D. Functionally distinct G proteins couple different receptors to PI hydrolysis in the same cell. *Cell* **56**, 487-493 (1989).

13. Ashkenazi, A., Ramachandran, J., and Capon, D. Acetylcholine analogue stimulates DNA synthesis in brain-derived cells via specific muscarinic acetylcholine receptor subtypes. *Nature* **340**, 146-150 (1989).

14. Lammare, D., Ashkenazi, A., Fleury, S., Smith, D., Sekaly, R., and Capon, D. The MHC-binding and gp120-binding domains of CD4 are distinct and separable. *Science* **245**, 743-745 (1989).

15. Ashkenazi., A., Presta, L., Marsters, S., Camerato, T., Rosenthal, K., Fendly, B., and Capon, D. Mapping the CD4 binding site for human immunodefficiency virus type 1 by alanine-scanning mutagenesis. *Proc. Natl. Acad. Sci. USA.* **87**, 7150-7154 (1990).

16. Chamow, S., Peers, D., Byrn, R., Mulkerrin, M., Harris, R., Wang, W., Bjorkman, P., Capon, D., and Ashkenazi, A. Enzymatic cleavage of a CD4 immunoadhesin generates crystallizable, biologically active Fd-like fragments. *Biochemistry* **29**, 9885-9891 (1990).

17. Ashkenazi, A., Smith, D., Marsters, S., Riddle, L., Gregory, T., Ho, D., and Capon, D. Resistance of primary isolates of human immunodefficiency virus type 1 to soluble CD4 is independent of CD4-rgp120 binding affinity. *Proc. Natl. Acad. Sci. USA.* **88**, 7056-7060 (1991).

18. Ashkenazi, A., Marsters, S., Capon, D., Chamow, S., Figari., I., Pennica, D., Goeddel., D., Palladino, M., and Smith, D. Protection against endotoxic shock by a tumor necrosis factor receptor immunoadhesin. *Proc. Natl. Acad. Sci. USA.* **88**, 10535-10539 (1991).

19. Moore, J., McKeating, J., Huang, Y., Ashkenazi, A., and Ho, D. Virions of primary HIV-1 isolates resistant to sCD4 neutralization differ in sCD4 affinity and glycoprotein gp120 retention from sCD4-sensitive isolates. *J. Virol.* **66**, 235-243 (1992).

20. Jin, H., Oksenberg, D., Ashkenazi, A., Peroutka, S., Duncan, A., Rozmahel., R., Yang, Y., Mengod, G., Palacios, J., and O'Dowd, B. Characterization of the human 5-hydroxytryptamine$_{1B}$ receptor. *J. Biol. Chem.* **267**, 5735-5738 (1992).

21. Marsters, A., Frutkin, A., Simpson, N., Fendly, B. and Ashkenazi, A. Identification of cysteine-rich domains of the type 1 tumor necrosis receptor involved in ligand binding. *J. Biol. Chem.* **267**, 5747-5750 (1992).

22. Chamow, S., Kogan, T., Peers, D., Hastings, R., Byrn, R., and Ashkenazi, A. Conjugation of sCD4 without loss of biological activity via a novel carbohydrate-directed cross-linking reagent. *J. Biol. Chem.* **267**, 15916-15922 (1992).

23. Oksenberg, D., Marsters, A., O'Dowd, B., Jin, H., Havlik, S., Peroutka, S., and Ashkenazi, A. A single amino-acid difference confers major pharmacologic variation between human and rodent 5-HT$_{1B}$ receptors. *Nature* **360**, 161-163 (1992).

24. Haak-Frendscho, M., Marsters, S., Chamow, S., Peers, D., Simpson, N., and Ashkenazi, A. Inhibition of interferon γ by an interferon γ receptor immunoadhesin. *Immunology* **79**, 594-599 (1993).

25. Penica, D., Lam, V., Weber, R., Kohr, W., Basa, L., Spellman, M., Ashkenazi, Shire, S., and Goeddel, D. Biochemical characterization of the extracellular domain of the 75-kd tumor necrosis factor receptor. *Biochemistry* **32**, 3131-3138. (1993).

26. Barfod, L., Zheng, Y., Kuang, W., Hart, M., Evans, T., Cerione, R., and Ashkenazi, A. Cloning and expression of a human CDC42 GTPase Activating Protein reveals a functional SH3-binding domain. *J. Biol. Chem.* **268**, 26059-26062 (1993).

27. Chamow, S., Zhang, D., Tan, X., Mhtre, S., Marsters, S., Peers, D., Byrn, R., Ashkenazi, A., and Yunghans, R. A humanized bispecific immunoadhesin-antibody that retargets CD3+ effectors to kill HIV-1-infected cells. *J. Immunol.* **153**, 4268-4280 (1994).

28. Means, R., Krantz, S., Luna, J., Marsters, S., and Ashkenazi, A. Inhibition of murine erythroid colony formation in vitro by iterferon γ and correction by interferon γ receptor immunoadhesin. *Blood* **83**, 911-915 (1994).

29. Haak-Frendscho, M., Marsters, S., Mordenti, J., Gillet, N., Chen, S., andAshkenazi, A. Inhibition of TNF by a TNF receptor immunoadhesin: comparison with an anti-TNF mAb. *J. Immunol.* **152**, 1347-1353 (1994).

30. Chamow, S., Kogan, T., Venuti, M., Gadek, T., Peers, D., Mordenti, J., Shak, S., and Ashkenazi, A. Modification of CD4 immunoadhesin with monomethoxy-PEG aldehyde via reductive alkilation. *Bioconj. Chem.* 5, 133-140 (1994).

31. Jin, H., Yang, R., Marsters, S., Bunting, S., Wurm, F., Chamow, S., and Ashkenazi, A. Protection against rat endotoxic shock by p55 tumor necrosis factor (TNF) receptor immunoadhesin: comparison to anti-TNF monoclonal antibody. *J. Infect. Diseases* **170**, 1323-1326 (1994).

32. Beck, J., Marsters, S., Harris, R., Ashkenazi, A., and Chamow, S. Generation of soluble interleukin-1 receptor from an immunoadhesin by specific cleavage. *Mol. Immunol.* **31**, 1335-1344 (1994).

33. Pitti, B., Marsters, M., Haak-Frendscho, M., Osaka, G., Mordenti, J., Chamow, S., and Ashkenazi, A. Molecular and biological properties of an interleukin-1 receptor immunoadhesin. *Mol. Immunol.* **31**, 1345-1351 (1994).

34. Oksenberg, D., Havlik, S., Peroutka, S., and Ashkenazi, A. The third intracellular loop of the 5-HT2 receptor specifies effector coupling. *J. Neurochem.* 64, 1440-1447 (1995).

35. Bach, E., Szabo, S., Dighe, A., Ashkenazi, A., Aguet, M., Murphy, K., and Schreiber, R. Ligand-induced autoregulation of IFN-γ receptor β chain expression in T helper cell subsets. *Science* **270**, 1215-1218 (1995).

36. Jin, H., Yang, R., Marsters, S., Ashkenazi, A., Bunting, S., Marra, M., Scott, R., and Baker, J. Protection against endotoxic shock by bactericidal/permeability-increasing protein in rats. *J. Clin. Invest.* 95, 1947-1952 (1995).

37. Marsters, S., Penica, D., Bach, E., Schreiber, R., and Ashkenazi, A. Interferon γ signals via a high-affinity multisubunit receptor complex that contains two types of polypeptide chain. *Proc. Natl. Acad. Sci. USA.* **92**, 5401-5405 (1995).

38. Van Zee, K., Moldawer, L., Oldenburg, H., Thompson, W., Stackpole, S., Montegut, W., Rogy, M., Meschter, C., Gallati, H., Schiller, C., Richter, W., Loetcher, H., Ashkenazi, A., Chamow, S., Wurm, F., Calvano, S., Lowry, S., and Lesslauer, W. Protection against lethal E. coli bacteremia in baboons by pretreatment with a 55-kDa TNF receptor-Ig fusion protein, Ro45-2081. *J. Immunol.* **156**, 2221-2230 (1996).

39. Pitti, R., Marsters, S., Ruppert, S., Donahue, C., Moore, A., and Ashkenazi, A. Induction of apoptosis by Apo-2 Ligand, a new member of the tumor necrosis factor cytokine family. *J. Biol. Chem.* 271, 12687-12690 (1996).

40. Marsters, S., Pitti, R., Donahue, C., Rupert, S., Bauer, K., and Ashkenazi, A. Activation of apoptosis by Apo-2 ligand is independent of FADD but blocked by CrmA. *Curr. Biol.* 6, 1669-1676 (1996).

41. Marsters, S., Skubatch, M., Gray, C., and Ashkenazi, A. Herpesvirus entry mediator, a novel member of the tumor necrosis factor receptor family, activates the NF-κB and AP-1 transcription factors. *J. Biol. Chem.* 272, 14029-14032 (1997).

42. Sheridan, J., Marsters, S., Pitti, R., Gurney, A., Skubatch, M., Baldwin, D., Ramakrishnan, L., Gray, C., Baker, K., Wood, W.I., Goddard, A., Godowski, P., and Ashkenazi, A. Control of TRAIL-induced apoptosis by a family of signaling and decoy receptors. *Science* 277, 818-821 (1997).

43. Marsters, S., Sheridan, J., Pitti, R., Gurney, A., Skubatch, M., Balswin, D., Huang, A., Yuan, J., Goddard, A., Godowski, P., and Ashkenazi, A. A novel receptor for Apo2L/TRAIL contains a truncated death domain. *Curr. Biol.* 7, 1003-1006 (1997).

44. Marsters, A., Sheridan, J., Pitti, R., Brush, J., Goddard, A., and Ashkenazi, A. Identification of a ligand for the death-domain-containing receptor Apo3. *Curr. Biol.* 8, 525-528 (1998).

45. Rieger, J., Naumann, U., Glaser, T., Ashkenazi, A., and Weller, M. Apo2 ligand: a novel weapon against malignant glioma? *FEBS Lett.* 427, 124-128 (1998).

46. Pender, S., Fell, J., Chamow, S., Ashkenazi, A., and MacDonald, T. A p55 TNF receptor immunoadhesin prevents T cell mediated intestinal injury by inhibiting matrix metalloproteinase production. *J. Immunol.* 160, 4098-4103 (1998).

47. Pitti, R., Marsters, S., Lawrence, D., Roy, Kischkel, F., M., Dowd, P., Huang, A., Donahue, C., Sherwood, S., Baldwin, D., Godowski, P., Wood, W., Gurney, A., Hillan, K., Cohen, R., Goddard, A., Botstein, D., and Ashkenazi, A. Genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer. *Nature* 396, 699-703 (1998).

48. Mori, S., Marakami-Mori, K., Nakamura, S., Ashkenazi, A., and Bonavida, B. Sensitization of AIDS Kaposi's sarcoma cells to Apo-2 ligand-induced apoptosis by actinomycin D. *J. Immunol.* 162, 5616-5623 (1999).

49. Gurney, A. Marsters, S., Huang, A., Pitti, R., Mark, M., Baldwin, D., Gray, A., Dowd, P., Brush, J., Heldens, S., Schow, P., Goddard, A., Wood, W., Baker, K., Godowski, P., and Ashkenazi, A. Identification of a new member of the tumor necrosis factor family and its receptor, a human ortholog of mouse GITR. *Curr. Biol.* 9, 215-218 (1999).

50. Ashkenazi, A., Pai, R., Fong, s., Leung, S., Lawrence, D., Marsters, S., Blackie, C., Chang, L., McMurtrey, A., Hebert, A., DeForge, L., Khoumenis, I., Lewis, D., Harris, L., Bussiere, J., Koeppen, H., Shahrokh, Z., and Schwall, R. Safety and anti-tumor activity of recombinant soluble Apo2 ligand. *J. Clin. Invest.* **104**, 155-162 (1999).

51. Chuntharapai, A., Gibbs, V., Lu, J., Ow, A., Marsters, S., Ashkenazi, A., De Vos, A., Kim, K.J. Determination of residues involved in ligand binding and signal transmissiion in the human IFN-α receptor 2. *J. Immunol.* **163**, 766-773 (1999).

52. Johnsen, A.-C., Haux, J., Steinkjer, B., Nonstad, U., Egeberg, K., Sundan, A., Ashkenazi, A., and Espevik, T. Regulation of Apo2L/TRAIL expression in NK cells – involvement in NK cell-mediated cytotoxicity. *Cytokine* **11**, 664-672 (1999).

53. Roth, W., Isenmann, S., Naumann, U., Kugler, S., Bahr, M., Dichgans, J., Ashkenazi, A., and Weller, M. Eradication of intracranial human malignant glioma xenografts by Apo2L/TRAIL. *Biochem. Biophys. Res. Commun.* **265**, 479-483 (1999).

54. Hymowitz, S.G., Christinger, H.W., Fuh, G., Ultsch, M., O'Connell, M., Kelley, R.F., Ashkenazi, A. and de Vos, A.M. Triggering Cell Death: The Crystal Structure of Apo2L/TRAIL in a Complex with Death Receptor 5. *Molec. Cell* **4**, 563–571 (1999).

55. Hymowitz, S.G., O'Connel, M.P., Utsch, M.H., Hurst, A., Totpal, K., Ashkenazi, A., de Vos, A.M., Kelley, R.F. A unique zinc-binding site revealed by a high-resolution X-ray structure of homotrimeric Apo2L/TRAIL. *Biochemistry* **39**, 633-640 (2000).

56. Zhou, Q., Fukushima, P., DeGraff, W., Mitchell, J.B., Stetler-Stevenson, M., Ashkenazi, A., and Steeg, P.S. Radiation and the Apo2L/TRAIL apoptotic pathway preferentially inhibit the colonization of premalignant human breast cancer cells overexpressing cyclin D1. *Cancer Res.* **60**, 2611-2615 (2000).

57. Kischkel, F.C., Lawrence, D. A., Chuntharapai, A., Schow, P., Kim, J., and Ashkenazi, A. Apo2L/TRAIL-dependent recruitment of endogenous FADD and Caspase-8 to death receptors 4 and 5. *Immunity* **12**, 611-620 (2000).

58. Yan, M., Marsters, S.A., Grewal, I.S., Wang, H., *Ashkenazi, A., and *Dixit, V.M. Identification of a receptor for BlyS demonstrates a crucial role in humoral immunity. *Nature Immunol.* **1**, 37-41 (2000).

59. Marsters, S.A., Yan, M., Pitti, R.M., Haas, P.E., Dixit, V.M., and Ashkenazi, A. Interaction of the TNF homologues BLyS and APRIL with the TNF receptor homologues BCMA and TACI. *Curr. Biol.* 10, 785-788 (2000).

60. Kischkel, F.C., and Ashkenazi, A. Combining enhanced metabolic labeling with immunoblotting to detect interactions of endogenous cellular proteins. *Biotechniques* 29, 506-512 (2000).

61. Lawrence, D., Shahrokh, Z., Marsters, S., Achilles, K., Shih, D. Mounho, B., Hillan, K., Totpal, K. DeForge, L., Schow, P., Hooley, J., Sherwood, S., Pai, R., Leung, S., Khan, L., Gliniak, B., Bussiere, J., Smith, C., Strom, S., Kelley, S., Fox, J., Thomas, D., and Ashkenazi, A. Differential hepatocyte toxicity of recombinant Apo2L/TRAIL versions. *Nature Med.* 7, 383-385 (2001).

62. Chuntharapai, A., Dodge, K., Grimmer, K., Schroeder, K., Martsters, S.A., Koeppen, H., Ashkenazi, A., and Kim, K.J. Isotype-dependent inhibition of tumor growth in vivo by monoclonal antibodies to death receptor 4. *J. Immunol.* 166, 4891-4898 (2001).

63. Pollack, I.F., Erff, M., and Ashkenazi, A. Direct stimulation of apoptotic signaling by soluble Apo2L/tumor necrosis factor-related apoptosis-inducing ligand leads to selective killing of glioma cells. *Clin. Cancer Res.* 7, 1362-1369 (2001).

64. Wang, H., Marsters, S.A., Baker, T., Chan, B., Lee, W.P., Fu, L., Tumas, D., Yan, M., Dixit, V.M., *Ashkenazi, A., and *Grewal, I.S. TACI-ligand interactions are required for T cell activation and collagen-induced arthritis in mice. *Nature Immunol.* 2, 632-637 (2001).

65. Kischkel, F.C., Lawrence, D. A., Tinel, A., Virmani, A., Schow, P., Gazdar, A., Blenis, J., Arnott, D., and Ashkenazi, A. Death receptor recruitment of endogenous caspase-10 and apoptosis initiation in the absence of caspase-8. *J. Biol. Chem.* 276, 46639-46646 (2001).

66. LeBlanc, H., Lawrence, D.A., Varfolomeev, E., Totpal, K., Morlan, J., Schow, P., Fong, S., Schwall, R., Sinicropi, D., and Ashkenazi, A Tumor cell resistance to death receptor induced apoptosis through mutational inactivation of the proapoptotitc Bcl-2 homolog Bax. *Nature Med.* 8, 274-281 (2002).

67. Miller, K., Meng, G., Liu, J., Hurst, A., Hsei, V., Wong, W-L., Ekert, R., Lawrence, D., Sherwood, S., DeForge, L., Gaudreault., Keller, G., Sliwkowski, M., Ashkenazi, A., and Presta, L. Design, Construction, and analyses of multivalent antibodies. *J. Immunol.* 170, 4854-4861 (2003).

68. Varfolomeev, E., Kischkel, F., Martin, F., Wanh, H., Lawrence, D., Olsson, C., Tom, L., Erickson, S., French, D., Schow, P., Grewal, I. and Ashkenazi, A. Immune system development in APRIL knockout mice. Submitted.

Review articles:

1. Ashkenazi, A., Peralta, E., Winslow, J., Ramachandran, J., and Capon, D., J. Functional role of muscarinic acetylcholine receptor subtype diversity. *Cold Spring Harbor Symposium on Quantitative Biology.* **LIII**, 263-272 (1988).
2. Ashkenazi, A., Peralta, E., Winslow, J., Ramachandran, J., and Capon, D. Functional diversity of muscarinic receptor subtypes in cellular signal transduction and growth. *Trends Pharmacol. Sci.* Dec Supplement, 12-21 (1989).
3. Chamow, S., Duliège, A., Ammann, A., Kahn, J., Allen, D., Eichberg, J., Byrn, R., Capon, D., Ward, R., and Ashkenazi, A. CD4 immunoadhesins in anti-HIV therapy: new developments. *Int. J. Cancer* Supplement 7, 69-72 (1992).
4. Ashkenazi, A., Capon, and D. Ward, R. Immunoadhesins. *Int. Rev. Immunol.* **10**, 217-225 (1993).
5. Ashkenazi, A., and Peralta, E. Muscarinic Receptors. In *Handbook of Receptors and Channels*. (S. Peroutka, ed.), CRC Press, Boca Raton, Vol. I, p. 1-27, (1994).
6. Krantz, S. B., Means, R. T., Jr., Lina, J., Marsters, S. A., and Ashkenazi, A. Inhibition of erythroid colony formation in vitro by gamma interferon. In *Molecular Biology of Hematopoiesis* (N. Abraham, R. Shadduck, A. Levine F. Takaku, eds.) Intercept Ltd. Paris, Vol. 3, p. 135-147 (1994).
7. Ashkenazi, A. Cytokine neutralization as a potential therapeutic approach for SIRS and shock. *J. Biotechnology in Healthcare* **1**, 197-206 (1994).
8. Ashkenazi, A., and Chamow, S. M. Immunoadhesins: an alternative to human monoclonal antibodies. *Immunomethods: A companion to Methods in Enzimology* **8**, 104-115 (1995).
9. Chamow, S., and Ashkenazi, A. Immunoadhesins: Principles and Applications. *Trends Biotech.* **14**, 52-60 (1996).
10. Ashkenazi, A., and Chamow, S. M. Immunoadhesins as research tools and therapeutic agents. *Curr. Opin. Immunol.* **9**, 195-200 (1997).
11. Ashkenazi, A., and Dixit, V. Death receptors: signaling and modulation. *Science* **281**, 1305-1308 (1998).
12. Ashkenazi, A., and Dixit, V. Apoptosis control by death and decoy receptors. *Curr. Opin. Cell. Biol.* **11**, 255-260 (1999).

13. Ashkenazi, A. Chapters on Apo2L/TRAIL; DR4, DR5, DcR1, DcR2; and DcR3. Online Cytokine Handbook (www.apnet.com/cytokinereference/).
14. Ashkenazi, A. Targeting death and decoy receptors of the tumor necrosis factor superfamily. *Nature Rev. Cancer* 2, 420-430 (2002).
15. LeBlanc, H. and Ashkenazi, A. Apoptosis signaling by Apo2L/TRAIL. *Cell Death and Differentiation* 10, 66-75 (2003).
16. Almasan, A. and Ashkenazi, A. Apo2L/TRAIL: apoptosis signaling, biology, and potential for cancer therapy. Cytokine and Growth Factor Reviews 14, 337-348 (2003).

Book:

Antibody Fusion Proteins (Chamow, S., and Ashkenazi. A., eds., John Wiley and Sons Inc.) (1999).

Talks:

1. Resistance of primary HIV isolates to CD4 is independent of CD4-gp120 binding affinity. UCSD Symposium, HIV Disease: Pathogenesis and Therapy. Greenelefe, FL, March 1991.
2. Use of immuno-hybrids to extend the half-life of receptors. IBC conference on Biopharmaceutical Halflife Extension. New Orleans, LA, June 1992.
3. Results with TNF receptor Immunoadhesins for the Treatment of Sepsis. IBC conference on Endotoxemia and Sepsis. Philadelphia, PA, June 1992.
4. Immunoadhesins: an alternative to human antibodies. IBC conference on Antibody Engineering. San Diego, CA, December 1993.
5. Tumor necrosis factor receptor: a potential therapeutic for human septic shock. American Society for Microbiology Meeting, Atlanta, GA, May 1993.
6. Protective efficiacy of TNF receptor immunoadhesin vs anti-TNF monoclonal antibody in a rat model for endotoxic shock. 5th International Congress on TNF. Asilomar, CA, May 1994.
7. Interferon-γ signals via a multisubunit receptor complex that contains two types of polypeptide chain. American Association of Immunologists Conference. San Franciso, CA, July 1995.
8. Immunoadhesins: Principles and Applications. Gordon Research Conference on Drug Delivery in Biology and Medicine. Ventura, CA, February 1996.

9. Apo-2 Ligand, a new member of the TNF family that induces apoptosis in tumor cells. Cambridge Symposium on TNF and Related Cytokines in Treatment of Cancer. Hilton-Head, NC, March 1996.
10. Induction of apoptosis by Apo2 Ligand. American Society for Biochemistry and Molecular Biology, Symposium on Growth Factors and Cytokine Receptors. New Orleans, LA, June, 1996.
11. Apo2 ligand, an extracellular trigger of apoptosis. 2nd Clontech Symposium, Palo Alto, CA, October 1996.
12. Regulation of apoptosis by members of the TNF ligand and receptor families. Stanford University School of Medicine, Palo Alto, CA, December 1996.
13. Apo-3: anovel receptor that regulates cell death and inflammation. 4th International Congress on Immune Consequences of Trauma, Shock, and Sepsis. Munich, Germany, March 1997.
14. New members of the TNF ligand and receptor families that regulate apoptosis, inflammation, and immunity. UCLA School of Medicine, LA, CA, March 1997.
15. Immunoadhesins: an alternative to monoclonal antibodies. 5th World Conference on Bispecific Antibodies. Volendam, Holland, June 1997.
16. Control of Apo2L signaling. Cold Spring Harbor Laboratory Symposium on Programmed Cell Death. Cold Spring Harbor, New York. September, 1997.
17. Chairman and speaker, Apoptosis Signaling session. IBC's 4th Annual Conference on Apoptosis. San Diego, CA., October 1997.
18. Control of Apo2L signaling by death and decoy receptors. American Association for the Advancement of Science. Philladelphia, PA, February 1998.
19. Apo2 ligand and its receptors. American Society of Immunologists. San Francisco, CA, April 1998.
20. Death receptors and ligands. 7th International TNF Congress. Cape Cod, MA, May 1998.
21. Apo2L as a potential therapeutic for cancer. UCLA School of Medicine. LA, CA, June 1998.
22. Apo2L as a potential therapeutic for cancer. Gordon Research Conference on Cancer Chemotherapy. New London, NH, July 1998.
23. Control of apoptosis by Apo2L. Endocrine Society Conference, Stevenson, WA, August 1998.
24. Control of apoptosis by Apo2L. International Cytokine Society Conference, Jerusalem, Israel, October 1998.

25. Apoptosis control by death and decoy receptors. American Association for Cancer Research Conference, Whistler, BC, Canada, March 1999.
26. Apoptosis control by death and decoy receptors. American Society for Biochemistry and Molecular Biology Conference, San Francisco, CA, May 1999.
27. Apoptosis control by death and decoy receptors. Gordon Research Conference on Apoptosis, New London, NH, June 1999.
28. Apoptosis control by death and decoy receptors. Arthritis Foundation Research Conference, Alexandria GA, Aug 1999.
29. Safety and anti-tumor activity of recombinant soluble Apo2L/TRAIL. Cold Spring Harbor Laboratory Symposium on Programmed Cell Death. . Cold Spring Harbor, NY, September 1999.
30. The Apo2L/TRAIL system: therapeutic potential. American Association for Cancer Research, Lake Tahoe, NV, Feb 2000.
31. Apoptosis and cancer therapy. Stanford University School of Medicine, Stanford, CA, Mar 2000.
32. Apoptosis and cancer therapy. University of Pennsylvania School of Medicine, Philladelphia, PA, Apr 2000.
33. Apoptosis signaling by Apo2L/TRAIL. International Congress on TNF. Trondheim, Norway, May 2000.
34. The Apo2L/TRAIL system: therapeutic potential. Cap-CURE summit meeting. Santa Monica, CA, June 2000.
35. The Apo2L/TRAIL system: therapeutic potential. MD Anderson Cancer Center. Houston, TX, June 2000.
36. Apoptosis signaling by Apo2L/TRAIL. The Protein Society, 14th Symposium. San Diego, CA, August 2000.
37. Anti-tumor activity of Apo2L/TRAIL. AAPS annual meeting. Indianapolis, IN Aug 2000.
38. Apoptosis signaling and anti-cancer potential of Apo2L/TRAIL. Cancer Research Institute, UC San Francisco, CA, September 2000.
39. Apoptosis signaling by Apo2L/TRAIL. Kenote address, TNF family Minisymposium, NIH. Bethesda, MD, September 2000.
40. Death receptors: signaling and modulation. Keystone symposium on the Molecular basis of cancer. Taos, NM, Jan 2001.
41. Preclinical studies of Apo2L/TRAIL in cancer. Symposium on Targeted therapies in the treatment of lung cancer. Aspen, CO, Jan 2001.

42. Apoptosis signaling by Apo2L/TRAIL. Wiezmann Institute of Science, Rehovot, Israel, March 2001.
43. Apo2L/TRAIL: Apoptosis signaling and potential for cancer therapy. Weizmann Institute of Science, Rehovot, Israel, March 2001.
44. Targeting death receptors in cancer with Apo2L/TRAIL. Cell Death and Disease conference, North Falmouth, MA, Jun 2001.
45. Targeting death receptors in cancer with Apo2L/TRAIL. Biotechnology Organization conference, San Diego, CA, Jun 2001.
46. Apo2L/TRAIL signaling and apoptosis resistance mechanisms. Gordon Research Conference on Apoptosis, Oxford, UK, July 2001.
47. Apo2L/TRAIL signaling and apoptosis resistance mechanisms. Cleveland Clinic Foundation, Cleveland, OH, Oct 2001.
48. Apoptosis signaling by death receptors: overview. International Society for Interferon and Cytokine Research conference, Cleveland, OH, Oct 2001.
49. Apoptosis signaling by death receptors. American Society of Nephrology Conference. San Francisco, CA, Oct 2001.
50. Targeting death receptors in cancer. Apoptosis: commercial opportunities. San Diego, CA, Apr 2002.
51. Apo2L/TRAIL signaling and apoptosis resistance mechanisms. Kimmel Cancer Research Center, Johns Hopkins University, Baltimore MD. May 2002.
52. Apoptosis control by Apo2L/TRAIL. (Keynote Address) University of Alabama Cancer Center Retreat, Birmingham, Ab. October 2002.
53. Apoptosis signaling by Apo2L/TRAIL. (Session co-chair) TNF international conference. San Diego, CA. October 2002.
54. Apoptosis signaling by Apo2L/TRAIL. Swiss Institute for Cancer Research (ISREC). Lausanne, Swizerland. Jan 2003.
55. Apoptosis induction with Apo2L/TRAIL. Conference on New Targets and Innovative Strategies in Cancer Treatment. Monte Carlo. February 2003.
56. Apoptosis signaling by Apo2L/TRAIL. Hermelin Brain Tumor Center Symposium on Apoptosis. Detroit, MI. April 2003.
57. Targeting apoptosis through death receptors. Sixth Annual Conference on Targeted Therapies in the Treatment of Breast Cancer. Kona, Hawaii. July 2003.
58. Targeting apoptosis through death receptors. Second International Conference on Targeted Cancer Therapy. Washington, DC. Aug 2003.

Issued Patents:

1. Ashkenazi, A., Chamow, S. and Kogan, T. Carbohydrate-directed crosslinking reagents. US patent 5,329,028 (Jul 12, 1994).
2. Ashkenazi, A., Chamow, S. and Kogan, T. Carbohydrate-directed crosslinking reagents. US patent 5,605,791 (Feb 25, 1997).
3. Ashkenazi, A., Chamow, S. and Kogan, T. Carbohydrate-directed crosslinking reagents. US patent 5,889,155 (Jul 27, 1999).
4. Ashkenazi, A., APO-2 Ligand. US patent 6,030,945 (Feb 29, 2000).
5. Ashkenazi, A., Chuntharapai, A., Kim, J., APO-2 ligand antibodies. US patent 6, 046, 048 (Apr 4, 2000).
6. Ashkenazi, A., Chamow, S. and Kogan, T. Carbohydrate-directed crosslinking reagents. US patent 6,124,435 (Sep 26, 2000).
7. Ashkenazi, A., Chuntharapai, A., Kim, J., Method for making monoclonal and cross-reactive antibodies. US patent 6,252,050 (Jun 26, 2001).
8. Ashkenazi, A. APO-2 Receptor. US patent 6,342,369 (Jan 29, 2002).
9. Ashkenazi, A. Fong, S., Goddard, A., Gurney, A., Napier, M., Tumas, D., Wood, W. A-33 polypeptides. US patent 6,410,708 (Jun 25, 2002).
10. Ashkenazi, A. APO-3 Receptor. US patent 6,462,176 B1 (Oct 8, 2002).
11. Ashkenazi, A. APO-2LI and APO-3 polypeptide antibodies. US patent 6,469,144 B1 (Oct 22, 2002).
12. Ashkenazi, A., Chamow, S. and Kogan, T. Carbohydrate-directed crosslinking reagents. US patent 6,582,928B1 (Jun 24, 2003).